SUPPLEMENT 168 — MAY 1997
Volume 106, Number 5, Part 2

CUK-H03721-43-P024717

FRONTIERS IN HEARING RESEARCH

Editors
GEORGE A. GATES, MD
EDWIN W RUBEL, PHD

43

ANNALS
OF OTOLOGY,
RHINOLOGY &
LARYNGOLOGY

FRONTIERS IN HEARING RESEARCH

Editors

GEORGE A. GATES, MD
EDWIN W RUBEL, PHD

P24717

43

Presented as a symposium at the opening ceremonies of the Virginia Merrill Bloedel Hearing Research Center, University of Washington, Seattle, Washington, July 7-8, 1995.

Additional copies of this publication are available from George A. Gates, MD, Virginia Merrill Bloedel Hearing Research Center, University of Washington, Box 357923, Seattle, WA 98195-7923, or may be purchased from Annals Publishing Company, 4507 Laclede Ave, St Louis, MO 63108.

COPYRIGHT© 1997, ANNALS PUBLISHING COMPANY

The Virginia Merrill Bloedel Hearing Research Center at the University of Washington would like to thank the following for their sponsorship of this publication.

BLOEDEL FAMILY TRUST

COCHLEAR CORPORATION

NATIONAL ORGANIZATION FOR HEARING RESEARCH

CONTENTS

Foreword
George A. Gates, MD; Edwin W Rubel, PhD 4

Prentice Bloedel 5

Virginia Merrill Bloedel 7

Hair Cell Regeneration in the Avian Cochlea
Douglas A. Cotanche, PhD 9

Outer Hair Cells: The Inside Story
Peter Dallos, PhD 16

Functional Asymmetries in the Auditory System
James Jerger, PhD 23

Neurobehavioral Studies of the Central Auditory System
R. Bruce Masterton, PhD 31

Speech Intelligibility of Children With Multichannel Cochlear Implants
Richard T. Miyamoto, MD; Mario Svirsky, PhD;
Karen Iler Kirk, PhD; Amy M. Robbins, MS;
Susan Todd, MS; Allison Riley, MS 35

Effects of Early Deafness on Development of Brain Stem Auditory Neurons
Thomas N. Parks, PhD 37

Roles of GABAergic Inhibition for the Binaural Processing of Multiple Sound Sources in the Inferior Colliculus
George D. Pollak, PhD 44

Eradication of Communicative Disorders: Preventive Medicine in the 21st Century
Robert J. Ruben, MD 55

Unravelling the Genetics of Deafness
Karen P. Steel, PhD; Philomena Mburu, PhD; Fernando Gibson, PhD;
James Walsh, BSc; Anabel Varela, BSc; Kathryn Brown, PhD; Tim Self, BSc;
Mary Mahony, PhD; Jane Fleming, PhD; Angela Pearce, BSc; David Harvey, PhD;
Jo Cable, PhD; Steve D. M. Brown, PhD 59

FOREWORD

The opening of the Virginia Merrill Bloedel Hearing Research Center at the University of Washington was a seminal event in the history of this institution. It was the culmination of a process begun in 1988, when a representative of the Bloedel family met with hearing scientists and clinicians from the Department of Otolaryngology–Head and Neck Surgery. The question asked at that meeting was, "How can we assure a lasting commitment of the University of Washington to research on hearing and deafness?" The answer, "Provide permanent positions and dedicated space."

This answer represents the faith of the Bloedel family in the power of modern biomedical science to bring a solution to a devastating hearing loss similar to that suffered by Virginia Merrill Bloedel for almost 20 years. This answer also represents the faith of enlightened university administrators who were willing to develop dedicated research space for investigations that cut across traditional departmental boundaries.

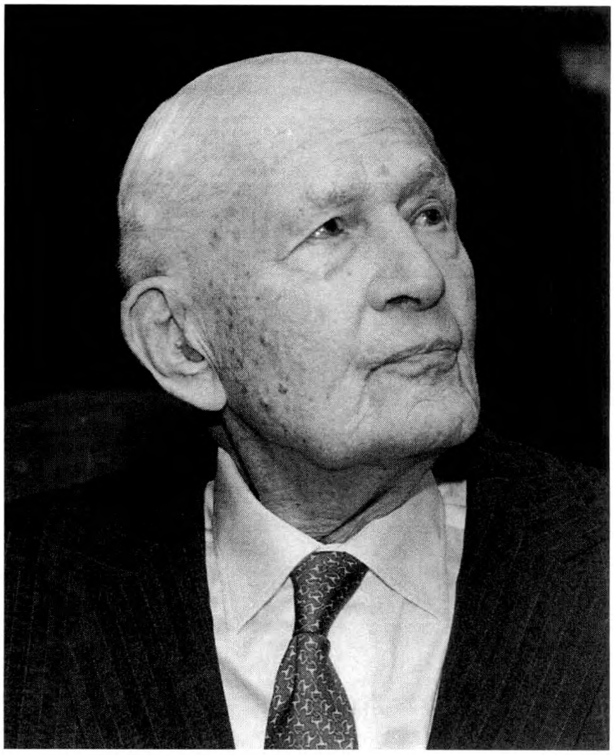
We have had the honor and privilege of being instrumental in the beginning of this Center, chairing the opening ceremonies, and participating in the scientific program commemorating its establishment. We would like to thank Drs Robert Dobie and Charles Cummings, who also played critical roles in the initial formulation of this Center.

The contents of this special issue represent the papers presented at the scientific symposium commemorating the opening of this new hearing center. This symposium was unique in its breadth. The participant-authors represent leaders in a broad range of fields, all of which are important for the understanding of hearing and the management of hearing disorders. The articles range from cutting-edge discoveries on the molecular genetics of hearing loss to new and traditional methods of diagnosis. They cut across traditional academic disciplines, deal with both peripheral and central processing, and shatter the archaic boundary between "clinical" and "basic" research. They represent but a sampling of the many issues and new discoveries that are rapidly advancing our understanding and that may lead to radical changes in the management of patients in the 21st century. We hope that you, the reader, will find these reviews of interest, and that they provide a spark for your own creative endeavors. We look forward to your comments and hope that you will be contributors to future symposia sponsored by the Virginia Merrill Bloedel Hearing Research Center.

Finally, we would like to thank the participants for taking the time from their busy schedules to participate in the symposium and prepare these articles. We also are greatly indebted to Linda C. Howarth and Leslie M. Sullivan for their efforts organizing the symposium and preparing this issue for publication.

George A. Gates, MD
Virginia Merrill Bloedel Professor of Clinical Research
Director, Virginia Merrill Bloedel Hearing Research Center

Edwin W Rubel, PhD
Virginia Merrill Bloedel Professor of Hearing Science



PRENTICE BLOEDEL

1900-1996

His name became as familiar in the Pacific Northwest as the trees upon which the family fortune was based. But family and friends say timber magnate and philanthropist Prentice Bloedel — a man who altered the face of Seattle during his long life — was a true gentleman, not one given to self-promotion.

Mr Bloedel died peacefully in his sleep in his home Saturday night, June 15, 1996, following a bout of pneumonia several months earlier. Mr Bloedel was 95. He was born in Bellingham, Washington, in 1900, within sight of his father's lumber mill on Lake Whatcom. After graduating from Yale University and marrying Virginia Merrill, daughter of another local timber family, Mr Bloedel returned to run his father's company in 1929.

Mr Bloedel was a principal founder of MacMillan Bloedel Ltd, a large Vancouver-based logging company that is a major supplier of newsprint, paper, and lumber to the United States. In addition to creating the Bloedel Conservatory, an indoor garden in Vancouver, Mr Bloedel contributed generously to organizations around Seattle. A long list of beneficiaries includes the Children's Hospital & Medical Center, the Seattle Art Museum, and the University of Washington. According to the family, Mr Bloedel's gifts enabled the University of Washington to build the Japanese Garden in the Washington Park Arboretum.

In 1988, moved by his wife's longtime hearing disorder, Mr Bloedel gave $5 million to the University for research into hearing impairments. This gift created the Virginia Merrill Bloedel Hearing Research Center at the University of Washington Medical Center. It was at the opening of the Center that the presentations printed herein were made on July 8, 1995.

In 1951, Mr Bloedel effectively retired and the family moved to Bainbridge Island in the Seattle area. It was there that Mr Bloedel and his wife lived in their French country house and began gardening. Eventually they cultivated the grounds into the 150-acre Bloedel Reserve, which opened to the public in 1988. The Reserve features a unique presentation of trees, shrubs, flowering plants, moss, and other flora that show nature as art.

The Reserve has a calming grandeur that causes one to reflect on the imponderable mysteries of creation.

Mr Bloedel's wife of 62 years, Virginia Merrill Bloedel, died in 1989. He is survived by his daughters, Virginia Wright of Seattle and Eulalie Schneider of Geneva, Switzerland; 7 grandchildren; and 15 great-grandchildren. A memorial service for Mr Bloedel was held at St Mark's Cathedral in Seattle on June 24.

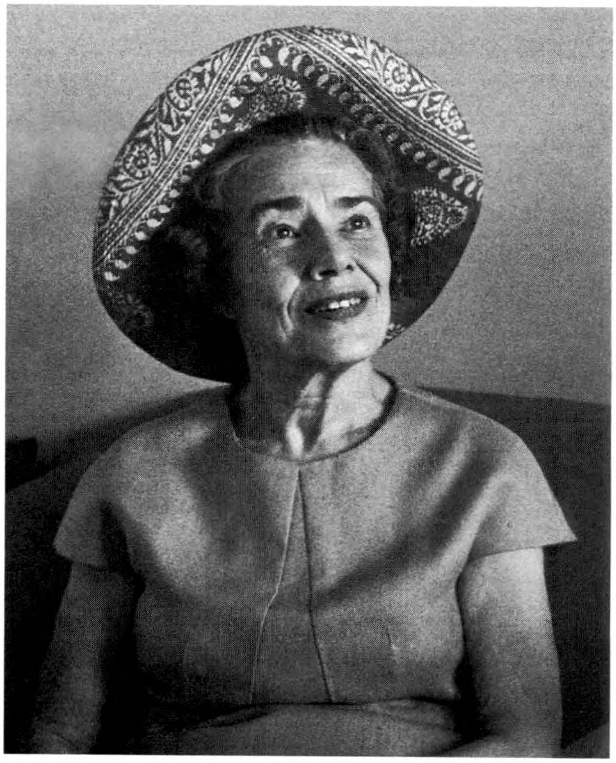
Eulogies presented there and published in the newspapers painted a picture of a quiet, contemplative man of high ideals, intense curiosity, scholarly interests, and an uncomplicated lifestyle. "He was a very private, measured man. He didn't offer his opinion freely, but he had a very simple code of ethics and he lived by it," said his son-in-law, Bagley Wright, founding president of the Seattle Repertory Theatre. Those ethics, Wright said, were based on "forthrightness and loyalties."

His younger daughter, Eulalie ("Lee") Schneider, recalled the depth of his vision for the future and his teaching of self-reliance to his children. His older daughter, Seattle art collector Virginia Wright, recalled her father as a serious and reflective man with wide intellectual interests ranging from science to poetry. "He had a noble kind of outlook," she said. Her father had suffered from polio as a young man, she said, and walked with a limp. She recalled her father taking her on a Christmas ski trip to Banff, in Alberta, Canada, even though he couldn't ski and had to sit around reading magazines. "It seemed like a very sweet, kind thing to do," she said.

A close friend, Seattle attorney John Hall, said Mr Bloedel was environmentally conscious, had long practiced replanting forests, and was very conservative in his use of clear-cutting. "He realized that man is just a part of nature," Hall said.

At the memorial service, former University President Bill Gerberding described Mr Bloedel's many contributions to the University and to the community, and recalled his gentle ways and quiet demeanor, his generosity and caring, and his fascination with science and the order of nature.

This uncommon man led an exemplary life that truly made the world a better place. He will be long remembered and sorely missed.



VIRGINIA MERRILL BLOEDEL

1902-1989

Although Virginia Merrill Bloedel passed away in 1989, her memory lives on through her family and friends. It also lives on in the form of the gardens of the Bloedel Reserve on Bainbridge Island and, now, in the Virginia Merrill Bloedel Hearing Research Center.

Virginia Merrill was born in 1902 in San Francisco and grew up in the Seattle area. As a child and young woman she was considered a tomboy, always active and fun to be with. She attended the Master's School in Dobbs Ferry, NY, and while there developed a love of literature, poetry, and theater. Her love of literature continued throughout her life and was a great comfort to her when her health started to fail late in life. Jane Austen, William Wordsworth, Robert Browning, Henry James, and Emily Bronte were among her favorite authors.

She married Prentice Bloedel, also a long-time resident of Seattle, in 1927. After living in Massachusetts for 2 years, they moved to Vancouver, Canada, so that Mr Bloedel could become involved with his family's timber business. It was there that Mrs Bloedel enjoyed a lively social life and formed many lifelong friendships.

Though she suffered from migraine headaches that frequently interfered with her activities, she enjoyed skiing and continued her golf game well into her 60s. She loved animals, especially dogs and horses, and was considered a skilled horsewoman. The main focus of her life was her strong belief in family values. She was devoted to her immediate family and to her large extended family who lived across the country. Family and friends were the focus of her loyalty and affection.

In the late 1940s the Bloedels learned of the availability of Collinswood on Bainbridge Island, which consisted of 67 acres of forest and a house. They immediately fell in love with the land and with the European-style home, which especially appealed to Mrs Bloedel because it reminded her of the lovely Swedish homes they had visited while abroad. Over the next 30 years, the property took shape: first as Agate Point Farm and then as the Bloedel Reserve. The Reserve is now open to the public and includes 150 acres of gardens, each carefully planned and lovingly cared for. It is, as Mr Bloedel explained, "a place apart from the hectic business, social and family worlds that fill our lives. It is a tranquil, spiritual place of retreat, open for meditation and rest — a place for the close and unrushed observations of the natural world."

The gardens show the love this couple felt for one another. Many of the features on the Reserve were given as gifts to each other; for example, the Swan Pond sitting area and the Christmas Pool were gifts to Mrs Bloedel and include her favorite flowers, trees, and shrubs; and the annual supply of trout placed in the Mid-Pond and the Bird Refuge were gifts to Mr Bloedel. The Glen, another gift and favorite spot for Mrs Bloedel, is a quiet, gentle place full of the colors and textures of the many rhododendrons, cyclamen, wild ginger, and other wildflowers growing there. Her gentle nature, thoughtfulness, and devotion are all seen and felt at the Reserve.

Mrs Bloedel's life was not always so tranquil, however. Not only did she suffer migraines throughout her life; during her last 15 to 20 years she also suffered from a progressive hearing loss. She was found, at the University of Washington Medical Center Otology Clinic, to have a moderately severe loss of hearing sensitivity accompanied by reduced speech understanding abilities in both ears. No medical or surgical treatment was available for her sensorineural loss, and the continued use of hearing aid amplification was recommended.

Although she wore hearing aids, they did not prevent her from experiencing the feelings of isolation, frustration, and strain that are often associated with hearing loss. Her frustrations grew because of an increasing inability to understand people, including her husband, unless they spoke directly to her. She often felt lost and alone in a group of people, as so many voices seemed mumbled and distorted. Since she had always been a very social person, her hearing difficulties interfered with her life more than other physical ailments. She relied more and more on lipreading to supplement her limited hearing. In spite of her inner torture, her natural grace, her love of literature, and the love of family and friends sustained her through these years.

When Mr and Mrs Bloedel learned of the exciting research on hearing being conducted at the University of Washington, they developed a plan to meld their love of the region with a desire to help others with hearing disorders. With the same sentiments that led them to open the Reserve to the public, the Bloedels wished to offer the community a brighter, richer environment. They chose to do this with endowment of a hearing research center. The Bloedels wished to assist scientists in their pursuit of remedies for hearing loss so that others would not have to suffer the isolation and frustration of this disability.

Virginia Merrill Bloedel's style, elegance, and love of learning will indeed live on through her friends and family, through the Bloedel Reserve, and, now, through the Virginia Merrill Bloedel Hearing Research Center.

Ann Otol Rhinol Laryngol 106:1997

HAIR CELL REGENERATION IN THE AVIAN COCHLEA

DOUGLAS A. COTANCHE, PHD
BOSTON, MASSACHUSETTS

Hair cell regeneration in the avian cochlea was first identified 10 years ago in studies of hair cell loss following noise damage and aminoglycoside treatment. Since then, numerous studies from several laboratories have examined a broad spectrum of the steps involved in the regeneration process. In this paper, we assess these studies and what they indicate about the events and regulatory mechanisms that control hair cell regeneration. Moreover, we examine how these studies have led to a reexamination of the possibility for hair cell regeneration in mammalian vestibular and cochlear sensory epithelia.

KEY WORDS — auditory function, avian, cochlea, hair cell, regeneration.

INTRODUCTION

Hair cell regeneration in the cochlear and vestibular systems of birds and mammals was virtually an unknown and unsuspected concept prior to 1987. It was assumed that hair cell loss in the mature epithelia of these higher vertebrates would lead to permanent structural and functional deficits. However, two studies published in 1987 suggested that the chick cochlea may have the potential to repair itself following noise- or aminoglycoside-induced damage to the sensory epithelium.[1,2] In the first study, the number of hair cells in the basilar papilla was assessed light microscopically at various time points following a 10-day administration of gentamicin.[1] There was an initial loss of most hair cells in the proximal half of the basilar papilla 1 week after the gentamicin administration. By 2 to 3 weeks, however, the number of hair cells in the proximal half of the cochlea had returned to 73% of normal levels, and it was concluded that this was caused by a regeneration of hair cells in the damaged region. The second study utilized scanning electron microscopy (SEM) to examine hair cell loss in the chick cochlea following pure tone noise exposure.[2] This study showed that a 48-hour noise exposure to a 1,500-Hz pure tone at 120 dB sound pressure level caused a large number of hair cells to be ejected from basilar papillae in the 1,500-Hz region. Two days after the end of the exposure, evidence of embryonic hair cells was seen in the region of hair cell loss. By 10 days of recovery, a large number of maturing hair cells had repopulated the area of hair cell loss (Fig 1). These observations led to the conclusion that new hair cells, or at least their stereociliary bundles, were being produced in a manner similar to that of normal embryonic development in order to replace those hair cells lost following the noise exposure. A parallel study demonstrated that the tectorial membrane was lost and regenerated in the region of hair cell damage in concert with the hair cells.[3]

These studies provided the first evidence that hair cells could be replaced following trauma-induced hair cell loss in the mature sensory epithelium. However, they did not indicate what cells were giving rise to the new hair cells, or how the new hair cells were produced. Since only supporting cells remained in the damaged region after the hair cell loss, it was hypothesized that the supporting cells divided to give rise to new hair cells. Two concurrent studies tested this hypothesis by giving injections of tritiated thymidine to hatchling chicks and adult quails during the recovery period following noise-induced hair cell loss.[4,5] In both studies, a large number of hair cells and adjacent supporting cells within the region of noise damage were labeled with tritiated thymidine when examined 7 to 10 days after the noise exposure. No labeling was seen in the basilar papilla outside the damaged regions or in control cochleas. These results confirmed that most, if not all, of the regenerated hair cells were produced by renewed cell divisions in the avian basilar papilla. Subsequent tritiated thymidine studies in chicks following gentamicin exposure indicated that this hair cell regeneration also arises from cell divisions in the cochlea.[6]

The demonstration that noise- or drug-induced

From the Department of Anatomy & Neurobiology, Boston University School of Medicine, Boston, Massachusetts. Supported by the National Institutes of Health/National Institute on Deafness and Other Communication Disorders and the National Organization for Hearing Research. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Boston University.

CORRESPONDENCE — Douglas A. Cotanche, PhD, Dept of Anatomy & Neurobiology, Boston University School of Medicine, 80 E Concord St, Boston, MA 02118.

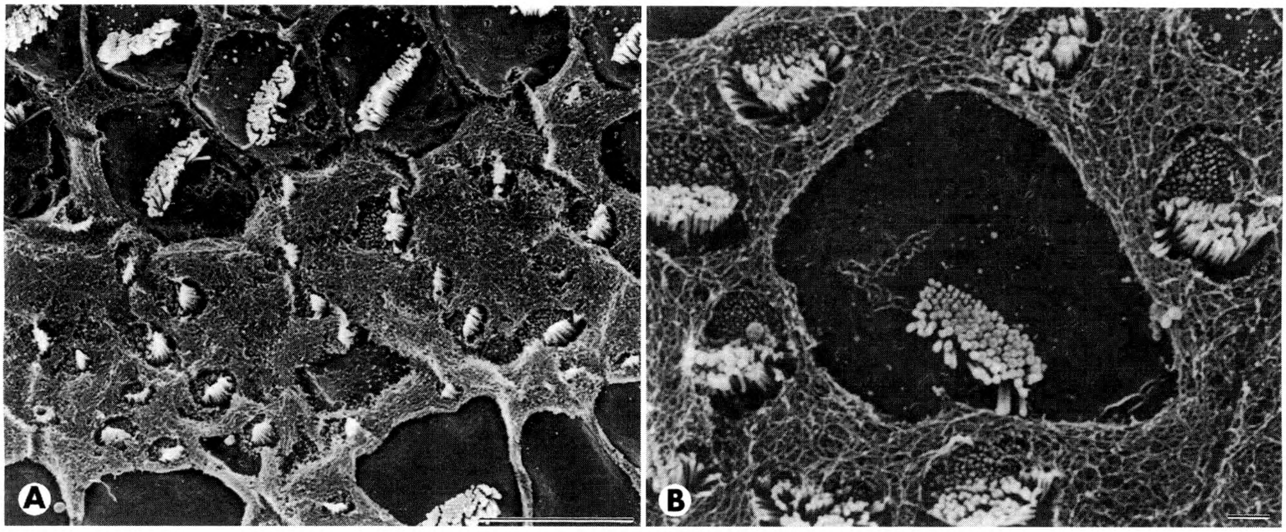


Fig 1. Scanning electron micrographs of new hair cells in chick cochlea following noise exposure. A) Numerous new hair cells are differentiating in region where hair cells had been lost from epithelium. Bar — 10 µm. B) Group of new hair cells surround one surviving hair cell. Bar — 1 µm.

hair cell loss led to the production of new hair cells in the avian cochlea sparked a revolution in our understanding of hair cell biology. Moreover, it stimulated investigators to question whether hair cell regeneration exists or can be induced in the mammalian vestibular and cochlear end organs. These initial findings on hair cell regeneration have attracted a number of research groups to enter the field and to explore the question with a wide range of structural, functional, and molecular approaches. This has resulted in more than 70 publications over the last 8 years; in the discovery that regeneration can occur in the vestibular epithelia of fish, amphibians, and birds; and in the discovery that at least the initial stages can occur in mammals, including humans. Evidence for regeneration in the neonatal rat organ of Corti has been presented, but at this time is still controversial.

While these studies have brought us a wealth of new information on regeneration in several vertebrate classes, a majority of the work has concentrated on regeneration in the avian cochlea. Studies at the structural, electrophysiologic, behavioral, and molecular levels have given us a rudimentary but fairly broad understanding of events in avian cochlear regeneration, from the onset of damage to the behaviorally significant recovery of function. We have recently surveyed the current literature on hair cell regeneration[7,8] to assess where the field has progressed to this point, and what areas appear to offer great promise for future studies. From these reviews, we have determined that the major events in avian cochlear hair cell regeneration can be broken down into five stages: 1) damage to the sensory epithelium that causes the loss of hair cells, 2) proliferation of supporting cells in response to the damage, 3) differentiation of the proliferated cells into hair cells and supporting cells, 4) maturation of the newly established cell types, and 5) functional recovery of the mature hair cells and supporting cells.

DAMAGE TO SENSORY EPITHELIUM

Regeneration in the avian basilar papilla occurs only after the sensory epithelium has been damaged. The two major techniques used for damaging the cochlea in recent research paradigms are noise exposure and aminoglycoside poisoning. Noise exposure produces a localized region of damage that is correlated with the frequency and intensity of the sound stimulus.[9-12] The initial response of the sensory epithelium to noise is a progressive shrinking of the hair cell surface area and a concomitant expansion of the surrounding supporting cell surfaces.[2,11-13] The damage begins initially at the inferior edge of the basilar papilla and moves superiorly with increasing exposure time or intensity. As the length or intensity of the stimulus increases further, some hair cells are ejected from the epithelium, especially in the region that overlies the junction of the basilar membrane with the superior fibrocartilaginous plate. The lost hair cells are replaced by further expansions of supporting cells.

Aminoglycoside treatment induces a hair cell loss that begins at the very proximal tip of the basilar papilla and moves distally with time and increasing drug dosage to involve 50% to 70% of the length of the cochlea.[1,14-18] Hair cells are ejected from the basilar papilla by blebbing up and out into the scala media and are phagocytosed by macrophage-like cells within the epithelium. They are replaced in the sensory epithelium by an expansion of adjacent supporting cell surfaces. In contrast to noise damage, after aminoglcoside damage there is no shrinkage of hair cell surfaces or concomitant expansion of supporting cell surfaces prior to the ejection of the hair cells.[8]

PROLIFERATION OF SUPPORTING CELLS

The avian basilar papilla responds to the loss of hair cells by inducing supporting cells in the area of hair cell loss to reenter the cell cycle and divide. Normally, the supporting cells in the post-hatching basilar papilla are quiescent and not dividing, especially in the proximal half of the cochlea.[4,19,20] However, within 18 to 24 hours after the onset of noise exposure or gentamicin administration, supporting cells in the area of hair cell loss begin to replicate their DNA.[16,20-24] Surprisingly, the onset of DNA synthesis in response to noise exposure begins at the same time regardless of whether the exposure is 4 or 24 hours in length.[20] Moreover, for the 24-hour exposures, DNA synthesis begins while the birds are still being exposed to the noise. A recent study examined markers for quiescent cells (G0), cells entering the first growth phase (G1), and cells entering the DNA synthesis phase (S) of the cell cycle after aminoglycoside treatment.[25] This study showed that a majority of the supporting cells throughout the basilar papilla leave G0 and enter into G1, but only those supporting cells in the areas where hair cells are lost make the transition from G1 to DNA synthesis. This suggests that while many of the supporting cells respond to the aminoglycoside, only those directly in contact with the injured or dying hair cells receive the signals that send them on through the entire cell cycle.

While the onset of DNA synthesis occurs between 18 and 24 hours after the start of the noise exposure, pulse labeling bromodeoxyuridine (BrdU) studies have shown that the peak of proliferation begins approximately 48 hours after the onset of the noise exposure.[20] For 24-hour noise exposures, this peak remains at a constant level out to 96 hours after the onset. In contrast, the peak after 4-hour exposures declines to very low levels by 72 hours after the onset. This pattern of proliferation is not surprising, since the 24-hour noise exposure induces much more hair cell loss than a 4-hour exposure. Similar pulse labeling experiments for the timing of DNA synthesis following aminoglycoside treatment have not been done, although multiple-injection BrdU studies have determined the broad pattern of proximal to distal DNA synthesis.[24]

The BrdU pulse studies were able to define the time when supporting cells undergo DNA synthesis prior to dividing. However, they did not directly demonstrate that these cells actually went on to become new hair cells after their mitoses. To show this, a single injection of BrdU was given 48 hours after the onset of noise exposure, and the birds were allowed to survive for 2 weeks before fixation and analysis of the tissues. Labeled hair cells were found at this time point; this finding indicates that the cells proliferating at 48 hours do go on to give rise to new hair cells.[20] Surprisingly, though, the number of labeled cells at this long recovery point was up to 8 times greater than when cochleas were analyzed 6 hours after a single injection at 48 hours after the onset of the noise. Control experiments and data from other studies showed that the BrdU was available to cells in S phase for only 4 to 6 hours after the injection, so this ruled out the possibility that the BrdU was being taken up by additional proliferating cells in the longer-recovery animals. In addition, the pattern of the labeling with increasing lengths of survival suggested that the original set of supporting cells that incorporated the BrdU went on to divide 2 or 3 more times during the 2-week recovery period. These data suggest that a single supporting cell can divide repeatedly to give rise to a number of daughter cells that can then go on to differentiate into either hair cells or supporting cells.[20]

Recent studies from our laboratory have used molecular biologic and immunocytochemical techniques to identify potential growth factors, retinoids, and their receptors that may be involved in regulating hair cell regeneration.[26] Polymerase chain reaction amplifications of specific messages from cochlear total RNA have shown that messenger RNAs for basic fibroblast growth factor (bFGF), fibroblast growth factor receptor (FGFR), and retinoic acid receptor ß (RARß) are present in both control cochleas and noise-damaged cochleas immediately after a 48-hour exposure. Immunocytochemical localization of the proteins these messages code for indicated that FGFR is found only in the nucleus of supporting cells, while RARß is present only in hair cell nuclei of both control and noise-exposed cochleas. The FGFR is expressed very faintly on the surfaces of supporting cells and around the bases of stereociliary bundles in control ears. In contrast, there is a heavy expression of FGFR on the expanded surfaces of supporting cells in the damaged region of noise-exposed cochleas. Thus, we hypothesize that supporting cells contain bFGF constitutively and are primed to respond to further activation by the binding of additional bFGF to the FGFRs expressed on the supporting cell surfaces following noise exposure.

DIFFERENTIATION OF NEW HAIR CELLS

Once a new pool of undifferentiated cells is created by the proliferation of supporting cells, these new cells must then differentiate down a pathway that leads to either new hair cells or new supporting cells. In noise damage studies, the first new hair cells appear 96 hours after the onset of noise exposure that lasts 4, 8, 12, 24, or 48 hours.[27] As recovery continues, more new hair cells appear after the longer exposures. This is not unexpected, since these cochleas lost more hair cells. In gentamicin studies, the first new hair cells appear in the most proximal region of the basilar papilla 3 to 5 days after a single injection of gentamicin.[16,28] With longer recoveries, new hair cells appear in more distal regions of the basilar papilla. Again, as with noise, the pattern and timing of new hair cell differentiation parallel those of both hair cell loss and supporting cell proliferation.

For both noise exposure and aminoglycoside treatment, the morphology of the new hair cell stereociliary bundles, as determined by SEM, is identical to that of the earliest stages of hair cell differentiation in the embryonic chick cochlea.[29,30] Moreover, these early regenerating bundles are similar to young embryonic hair cells in that they lack the organized bundle orientations of mature hair cells.[31,32]

To date, it has not been possible to identify when new supporting cells first differentiate in the regenerating basilar papilla. This is because there are no biochemical markers that clearly distinguish newly differentiated supporting cells from undifferentiated precursor cells or mature supporting cells that were already present in the epithelium. Furthermore, there are no distinct morphologic surface markers, such as the new stereociliary bundles on hair cells, to identify new supporting cells in SEM examinations.

MATURATION OF HAIR CELLS AND SUPPORTING CELLS

Once new hair cells differentiate, their stereociliary bundles continue to mature in a manner that again recapitulates embryonic development. First, the staircase pattern is established, then excess microvilli are eliminated and the bundle grows to the proper height for its position on the basilar papilla. Finally, the tallest row of stereocilia establishes connections with the regenerating tectorial membrane, and the correct orientation of the bundle is established. It has been known for some time that noise exposure also damages the tectorial membrane in the region of hair cell loss and that the membrane is regenerated in concert with the hair cells.[3,33-36] The new tectorial membrane is secreted by the supporting cells in the damaged region, forms a new honeycomb matrix around the regenerating hair cells, and eventually establishes connections with adjacent segments of undamaged tectorial membrane.

We have recently demonstrated that gentamicin treatment does not damage the structure of the tectorial membrane, but that the expulsion of dying hair cells from the basilar papilla severs the connections between the tectorial membrane and the supporting cells in the damaged region of the epithelium.[28] During subsequent hair cell regeneration, the supporting cells secrete a new basal layer of tectorial membrane that establishes connections with both the new hair cells and the overlying portion of the undamaged tectorial membrane. Several studies of hair cell regeneration following aminoglycoside treatment have noted that new hair cell stereociliary bundles never completely regain the uniform bundle orientation seen in undamaged basilar papillae.[16-18,37,38] This lack of complete reorientation may be due to the complete loss of hair cells in the proximal half of the basilar papilla and/or the need for a synthesis of an entirely new basal layer of tectorial membrane in this region.

The newly forming hair cells must also establish connections with both afferent and efferent nerve endings during their maturation to become functional. Noise damage studies have shown that new afferent and efferent endings do appear on regenerated hair cells and eventually establish adult-like innervation patterns.[39-41] Studies of reinnervation following gentamicin treatment have indicated that innervation of the new hair cells occurs in a pattern that reflects the normal development of innervation during embryogenesis.[14,37] Thus, the short hair cells, which normally receive no afferent innervation,[41] make transient connections with afferent endings in the early stages of regeneration, but lose these with time to eventually receive only efferent synapses.

While it has been established that regenerated hair cells make synaptic connections with both afferent and efferent nerves during recovery, it is not clear if these synapses are with the same fibers that innervated the original population of hair cells, or if they arise from different fibers. Preliminary studies in our laboratory have examined nerve fiber patterns in whole mount preparations of control and noise-damaged chick basilar papillae by labeling with antibodies to neurofilament proteins.[42] These experiments have demonstrated that the overall nerve fiber distribution is not altered by levels of noise damage that induce hair cell regeneration. However, it is still not known whether the small nerve branches that extend from the nerve bundles to the hair cells are retained after noise exposure, or if they must develop anew.

FUNCTIONAL RECOVERY

While the regeneration of hair cells in the chick

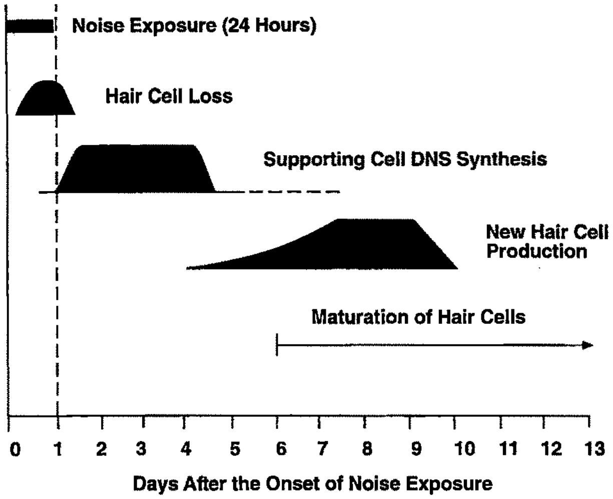


Fig 2. Chart of temporal sequence of events in hair cell regeneration following noise exposure. Regeneration following aminoglycoside treatment follows similar sequence, except that initial trauma may last up to 10 days.

Epithelium	Damage	Prolif.	Diff.	Mat.	Func. Rec.
Avian Cochlea	√	√	√	√	√
Avian Vestibule	√	√	√	√	√
Mammalian Cochlea	√	?	√	?	?
Mammalian Vestibule	√	√	√	?	?

Fig 3. Chart of five stages in hair cell regeneration for cochlear and vestibular epithelia of birds and mammals. √ — documented in this epithelium, ? — not tested or unclear for this epithelium, Prolif. — proliferation, Diff. — differentiation, Mat. — maturation, Func. Rec. — functional recovery.

basilar papilla is an interesting model system for examining the regulation of cell proliferation and differentiation, it is not of much significance to the bird unless it leads to the reestablishment of biologically significant auditory function. Electrophysiologic recordings from the brain stem of chicks following noise exposure have demonstrated that initial threshold shifts of 50 to 60 dB recover to near-normal levels within 3 to 10 days after the end of the noise exposure.[36,43-46] A significant amount of this recovery occurs before the regenerating hair cells reach maturity, and this finding has been attributed to the fact that noise exposure damages predominantly the short hair cells that receive no afferent innervation.[44] Thus, the initial stages of recovery may be due to rapid recovery of transduction in tall hair cells. The functional role of short hair cell regeneration following noise exposure has not yet been explored in significant detail.

Electrophysiologic studies of functional recovery following aminoglycoside treatment have shown that thresholds recover to near-normal levels over a 4- to 20-week period.[15,47] This protracted period of recovery is most probably due to the fact that aminoglycosides destroy most, if not all, of the tall and short hair cells in the proximal half of the basilar papilla. Thus, all the hair cells and their synaptic connections must be reestablished before functional activity can return.

Recent experiments have used behavioral measures to test functional recovery following noise exposure or aminoglycoside treatment.[38,48,49] Since behavioral tests are noninvasive and can be done repeatedly on the same animal, they are especially suitable for longitudinal studies tracing the initial extent of functional loss and the timing and extent of recovery. These studies have shown that birds are capable of recovery to near-normal threshold levels by 8 to 10 days after a noise exposure[48] or by 50 days after aminoglycoside treatment.[38] Exposure to 2 or 3 further rounds of noise trauma led to equivalent levels of recovery, but each successive recovery took 1 to 2 days longer than the previous one.[48] In contrast, a second aminoglycoside treatment led to less severe structural damage to the hair cells and a less extensive functional loss.[38] A subsequent study showed that the reduction in damage was due to an increased systemic ability to detoxify the aminoglycoside in the second exposure.[49] When blood levels of the drug were increased to match those of the first dose, the level of structural damage and threshold loss was equivalent to that of the first treatment. This indicates that the resistance to damage in the regenerated ear was based on the animal's systemic response to the aminoglycoside, rather than an increased resistance in the new hair cells.

Current behavioral studies are being designed to address more complex levels of auditory discrimination than just threshold shifts.[50] These studies should provide exciting new information about the level of auditory perception and discrimination in birds following regeneration of their hair cells.

CONCLUSIONS

Hair cell regeneration in the avian cochlea has been examined at multiple levels for both noise-exposed cochleas and cochleas treated with aminoglycosides. These studies from a number of laboratories have demonstrated that the regeneration involves damage to the existing hair cells, proliferation of surviving supporting cells, differentiation of new hair cells and supporting cells, maturation of the new components within the receptor epithelium, and recovery of auditory function. While there are specific aspects of regeneration following noise exposure that differ from regeneration following aminoglycoside treatment, the overall patterns are quite similar (Fig 2). This suggests that the basic mechanisms used to repair the damaged epithelium represent a default cascade of events that are set in motion by hair cell loss regardless of how that hair cell loss occurs. Thus, if the steps that initiate this process can be isolated and defined, it should be possible to regulate regeneration experimentally. One hopes that future studies will define the triggers that initiate the process.

Studies of hair cell regeneration in vestibular or auditory epithelia of other species have defined some events that are similar to those in the avian cochlea (Fig 3). Avian vestibular hair cell regeneration demonstrates all five of the stages of regeneration identified in the cochlea.[51-55] Mammalian vestibular epithelia show signs of hair cell loss, supporting cell proliferation, and new hair cell production, although the precise connection between these events has not been clearly established.[56-58] Hair cell regeneration in the neonatal rat cochlea has been proposed, but the interpretations of these studies are still controversial.[59-61]

While much work remains to be done to fully understand the process of hair cell regeneration in higher vertebrates, the serendipitous findings of cochlear hair cell regeneration in the bird have stimulated a renewed interest in the possibility that regeneration offers a therapeutic treatment for deafness or balance disorders that result from hair cell loss.

ACKNOWLEDGMENTS — The author expresses his appreciation to the Virginia Merrill Bloedel Hearing Research Center for inviting him to participate in the opening ceremonies for the Center. He especially thanks the students and technicians in his laboratory who have contributed so much to the progress of the laboratory over the last few years, and to his colleagues in the field who have provided provocative and stimulating new revelations on hair cell regeneration. In addition, the author thanks Linda Howarth for her editorial help.

REFERENCES

1. Cruz RM, Lambert PM, Rubel EW. Light microscopic evidence of hair cell regeneration after gentamicin toxicity in chick cochlea. Arch Otolaryngol Head Neck Surg 1987;113:1058-62.

2. Cotanche DA. Regeneration of hair cell stereociliary bundles in the chick cochlea following severe acoustic trauma. Hear Res 1987;30:181-96.

3. Cotanche DA. Regeneration of the tectorial membrane in the chick cochlea following severe acoustic trauma. Hear Res 1987;30:197-206.

4. Corwin JT, Cotanche DA. Regeneration of sensory hair cells after acoustic trauma. Science 1988;240:1772-4.

5. Ryals BM, Rubel EW. Hair cell regeneration after acoustic trauma in adult *Coturnix* quail. Science 1988;240:1774-6.

6. Lippe WR, Westbrook EW, Ryals BM. Hair cell regeneration in the chicken cochlea following aminoglycoside toxicity. Hear Res 1991;56:203-10.

7. Cotanche DA, Lee KH. Regeneration of hair cells in the vestibulocochlear system of birds and mammals. Curr Opin Neurobiol 1994;4:508-14.

8. Cotanche DA, Lee KH, Stone JS, Picard DA. Hair cell regeneration in the bird cochlea following noise damage or ototoxic drug damage: a review. Anat Embryol (Berl) 1994;189:1-18.

9. Rubel EW, Ryals BM. Patterns of hair cell loss in chick basilar papilla after intense auditory stimulation. Exposure duration and survival time. Acta Otolaryngol (Stockh) 1982;93:31-41.

10. Ryals BM, Rubel EW. Patterns of hair cell loss in the chick basilar papilla after intense auditory stimulation: frequency organization. Acta Otolaryngol (Stockh) 1982;93:205-10.

11. Cotanche DA, Saunders JC, Tilney LG. Hair cell damage produced by acoustic trauma in the chick cochlea. Hear Res 1987;25:267-86.

12. Cotanche DA, Dopyera CEJ. Hair cell and supporting cell response to acoustic trauma in the chick cochlea. Hear Res 1990; 46:29-40.

13. Raphael Y. Reorganization of the chick basilar papilla after acoustic trauma. J Comp Neurol 1993;330:521-32.

14. Duckert LG, Rubel EW. Ultrastructural observations on regenerating hair cells in the chick basilar papilla. Hear Res 1990;48:161-82.

15. Girod DA, Tucci DL, Rubel EW. Anatomical correlates of functional recovery in the avian inner ear following aminoglycoside ototoxicity. Laryngoscope 1991;101:1139-49.

16. Janas JD, Cotanche DA, Rubel EW. Avian cochlear hair cell regeneration: a stereological analysis of damage and recovery from single high dose of gentamicin. Hear Res 1995;92:17-29.

17. Hashino E, Tanaka Y, Sokabe M. Hair cell damage and recovery following chronic application of kanamycin in the chick cochlea. Hear Res 1991;52:356-68.

18. Hashino E, Tanaka Y, Salvi RJ, Sokabe M. Hair cell regeneration in the adult budgerigar after kanamycin ototoxicity. Hear Res 1992;59:46-58.

19. Oesterle EC, Rubel EW. Postnatal production of supporting cells in the chick cochlea. Hear Res 1993;66:213-24.

20. Stone JS, Cotanche DA. Identification of the timing of S phase and the patterns of cell proliferation during hair cell regeneration in the chick cochlea. J Comp Neurol 1994;341:50-67.

21. Girod DA, Duckert LG, Rubel EW. Possible precursors of regenerated hair cells in the avian cochlea following acoustic trauma. Hear Res 1989;42:175-94.

22. Raphael Y. Evidence for supporting cell mitosis in response to acoustic trauma in the avian inner ear. J Neurocytol 1992;21:663-71.

23. Hashino E, Salvi RJ. Changing spatial patterns of DNA replication in the noise-damaged chick cochlea. J Cell Sci 1993; 105:23-31.

24. Hashino E, TinHan E, Salvi RJ. Base-to-apex gradient of cell proliferation in the chick cochlea following kanamycin-induced hair cell loss. Hear Res 1995;88:156-68.

25. Bhave SA, Stone JS, Rubel EW, Coltrera MD. Cell cycle

progression in gentamicin-damaged avian cochleas. J Neurosci 1995;15:4618-28.

26. Lee KH, Cotanche DA. Potential role of bFGF and retinoic acid in the regeneration of chicken cochlear hair cells. Hear Res 1996;94:1-13.

27. Stone JS, Cotanche DA. Synchronization of hair cell regeneration in the chick cochlea following noise damage. J Cell Sci 1992;102:671-80.

28. Epstein JE, Cotanche DA. Secretion of a new basal layer of tectorial membrane following gentamicin induced hair cell loss. Hear Res 1995;90:31-43.

29. Cotanche DA, Sulik KK. The development of stereociliary bundles in the cochlear duct of chick embryos. Dev Brain Res 1984;16:181-93.

30. Cotanche DA. Development of hair cell stereocilia in the avian cochlea. Hear Res 1987;28:35-44.

31. Cotanche DA, Corwin JT. Stereociliary bundles reorient during hair cell development and regeneration in the chick cochlea. Hear Res 1991;52:379-402.

32. Cotanche DA, Petrell A, Picard DA. Structural reorganization of hair cells and supporting cells during noise damage, recovery and regeneration in the chick cochlea. In: Bock GR, Whelan J, eds. Regeneration of vertebrate sensory cells. Ciba Foundation Symposium 160. New York, NY: John Wiley & Sons, 1991:131-50.

33. Cotanche DA. Video-enhanced DIC images of the noise-damaged and regenerated chick tectorial membrane. Exp Neurol 1992;115:23-6.

34. Raphael Y. Pure tone overstimulation protects surviving avian hair cells from acoustic trauma. Hear Res 1991;53:173-84.

35. Adler HJ, Kenealy JFX, Dedio RM, Saunders JC. Threshold shift, hair cell loss, and hair bundle stiffness following exposure to 120 and 125 dB pure tones in the neonatal chick. Acta Otolaryngol (Stockh) 1992;112:444-54.

36. Adler HJ, Poje CP, Saunders JC. Recovery of auditory function and structure in the chick after two intense pure tone exposures. Hear Res 1993;71:214-24.

37. Duckert LG, Rubel EW. Morphological correlates of functional recovery in the chicken inner ear after gentamicin treatment. J Comp Neurol 1993;331:75-96.

38. Marean GC, Burt JM, Beecher MD, Rubel EW. Hair cell regeneration in the European starling (*Sturnus vulgaris*): recovery of pure tone detection thresholds. Hear Res 1993;71:125-36.

39. Ryals BM, Westbrook EW, Stoots S, Spencer RF. Changes in the acoustic nerve after hair cell regeneration. Exp Neurol 1992;115:18-22.

40. Ryals BM, Westbrook EW. TEM analysis of neural terminals on autoradiographically identified regenerated hair cells. Hear Res 1994;72:81-8.

41. Fischer FP. Quantitative analysis of the innervation of the chicken basilar papilla. Hear Res 1992;61:167-78.

42. Ofsie MS, Cotanche DA. Distribution of nerve fibers in the basilar papilla of normal and sound damaged chick cochleae. J Comp Neurol 1996;370:281-94.

43. McFadden EA, Saunders JC. Recovery of auditory function following intense sound exposure in the neonatal chick. Hear Res 1989;41:205-15.

44. Saunders JC, Adler HJ, Pugliano FA. The structural and functional aspects of hair cell regeneration in the chick as a result of exposure to intense sound. Exp Neurol 1992;115:13-7.

45. Pugliano FA, Wilcox TO, Rossiter J, Saunders JC. Recovery of auditory structure and function in neonatal chicks exposed to intense sound for 8 days. Neurosci Lett 1993;151:214-8.

46. Cohen YE, Saunders JC. The effects of sound overexposure on the spectral response patterns of nucleus magnocellularis in the neonatal chick. Exp Brain Res 1993;95:202-12.

47. Tucci DL, Rubel EW. Physiological status of regenerated hair cells in the avian inner ear following aminoglycoside ototoxicity. Otolaryngol Head Neck Surg 1990;103:443-50.

48. Niemiec AJ, Raphael Y, Moody DB. Return of auditory function following structural regeneration after acoustic trauma: behavioral measures from quail. Hear Res 1994;75:125-36.

49. Marean GC, Cunningham D, Burt JM, Beecher MD, Rubel EW. Regenerated hair cells in the European starling: are they more resistant to kanamycin ototoxicity than original hair cells? Hear Res 1995;82:267-76.

50. Ryals BM, Dooling RJ. Hair cell regeneration and the restoration of hearing. Assoc Res Otolaryngol Abstr 1995;18:146.

51. Jørgensen JM, Mathiesen C. The avian inner ear: continuous production of hair cells in vestibular sensory organs, but not in the auditory basilar papilla. Naturwissenschaften 1988;75:319-20.

52. Roberson DW, Weisleder P, Bohrer PS, Rubel EW. Ongoing production of sensory cells in the vestibular epithelium of the chick. Hear Res 1992;57:166-74.

53. Weisleder P, Rubel EW. Hair cell regeneration after streptomycin toxicity in the avian vestibular epithelium. J Comp Neurol 1993;331:97-110.

54. Jones TA, Nelson RC. Recovery of vestibular function following hair cell destruction by streptomycin. Hear Res 1992; 62:181-6.

55. Tsue TT, Watling DL, Weisleder P, Coltrera MD, Rubel EW. Identification of hair cell progenitors and intermitotic migration of their nuclei in the normal and regenerating avian inner ear. J Neurosci 1994;14:140-52.

56. Forge A, Li L, Corwin JT, Nevill G. Ultrastructural evidence for hair cell regeneration in the mammalian inner ear. Science 1993;259:1616-9.

57. Warchol ME, Lambert PR, Goldstein BJ, Forge A, Corwin JT. Regenerative proliferation in inner ear sensory epithelia from adult guinea pigs and humans. Science 1993;259:1619-22.

58. Rubel EW, Dew LA, Roberson DW. Mammalian vestibular hair cell regeneration. Science 1995;267:701-3.

59. LeFebvre PP, Malgrange B, Staecker H, Moonen G, Van De Water TR. Retinoic acid stimulates regeneration of mammalian auditory hair cells. Science 1993;260:692-5.

60. Chardin S, Romand R. Regeneration and mammalian auditory hair cells. Science 1995;267:707-11.

61. Kelley MW, Talreja DR, Corwin JT. Replacement of hair cells after laser microbeam irradiation in cultured organs of Corti from embryonic and neonatal mice. J Neurosci 1995;15:3013-26.

Ann Otol Rhinol Laryngol 106:1997

OUTER HAIR CELLS: THE INSIDE STORY

PETER DALLOS, PHD
EVANSTON, ILLINOIS

The neurobiology of hair cells is reviewed, including their transduction apparatus, the production and nature of receptor potentials, and the similarities and differences between inner hair cells and outer hair cells (OHCs). Intracellular recordings from hair cells in vivo are discussed. This is followed by a consideration of effects of OHC lesions and consequent notions about OHC functions. Feedback in the cochlea is then considered, and the role of OHCs as the feedback element is examined, along with putative means of producing the feedback.

KEY WORDS — cochlea, cochlear amplifier, hair cells, outer hair cell motility, receptor potentials.

I would liken the current state of auditory neurobiology to the way I give final examinations nowadays. I've noticed that students are extremely good at collecting information about past examinations, and dormitories and fraternities have wonderful files of past examinations, so it's very difficult to recycle questions. So, what I do is give exactly the same question year to year, but change the correct answer! And that, in fact, is how auditory neurobiology is, as you will see during this discussion. My emphasis is on mammalian hearing, not because I am parochial, but because that is, of course, what we are interested in from our own vantage point as human beings, because of our disorders, because of our difficulties, and because of our need to communicate.

I will talk about hair cells, the receptor cells of the auditory organ, in the context of the mechanics of the cochlea, and how the two interact and work together. The structures of importance to consider in the mammalian cochlea are the basilar membrane, which is a vibrating structure, the scala media compartment filled with endolymph, and the organ of Corti, which is the sense organ of hearing. Contained within the organ of Corti are two types of sensory receptor cells: outer hair cells and inner hair cells. These two types of cells will be the subject of my discussion, most specifically the outer hair cell and how it interacts with the surrounding structures in forming the mechanical response of the overall system.

Hair cells are epithelial cells, meaning that they are sealed between two different fluid compartments and they have two completely differently behaving segments. The apical part is surrounded by endolymph, and the basolateral part is surrounded by perilymph and supporting cells. The apical part of the cell contains the stereocilia, after which the hair cells are named. It is the deflection of these fine hairlike structures that delivers mechanical energy into the hair cell. It appears that the sensory input structure of all the types of hair cells among vertebrates is conserved. In other words, what seems to be happening in outer hair cells, inner hair cells, frog hair cells, any hair cells, is that there are shearing motions or displacements of these cilia. Adjacent stereocilia are connected to one another with extremely fine filaments, "tip links," which are arranged in a perfectly orderly geometric arrangement along the major axis of the stereociliary bundle. This was first found and emphasized by Jim Pickles.

The most commonly accepted hypothesis about these connections is that when the stereociliary bundle is bent by mechanical forces, these tip links are stretched as mechanical energy is delivered to them. When the mechanical energy is appropriately large, they physically open ion channels located somewhere in the stereocilia, permitting the abundantly available potassium ions from the endolymph to flow into the cell and thereby change its electrical configuration to produce a voltage drop on the cell membrane. So, the general hypothesis is that the modulation of the influx of potassium into the cell is the first important event in transduction, for the delivery of signals into the auditory system. This is often referred to as the receptor current. The current, of course, flows down its gradient into the surrounding fluid. As it does, it produces a voltage drop on the cell's basolateral membrane, and this is called the receptor

---

From the Auditory Physiology Laboratory, Northwestern University, Evanston, Illinois. Supported by grants from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Northwestern University.

CORRESPONDENCE—Peter Dallos, PhD, Auditory Physiology Laboratory, Frances Searle Building, Northwestern University, 2299 North Campus Dr, Evanston, IL 60208.

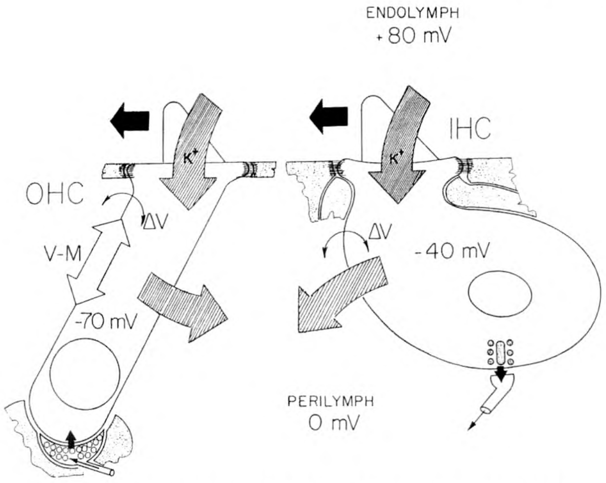


Fig 1. Drawing of outer (OHC) and inner hair cells (IHC) shown partitioned between positively polarized endolymph and zero-potential perilymph. Resting membrane potentials are shown as obtained with sharp microelectrodes in vivo. Potassium flux (cross-hatched arrows), bending of ciliary bundle, and mechanical input (black arrows) are indicated. ΔV — receptor potential. Motile response of OHC is symbolized by voltage-to-movement converter (V-M). At synaptic pole of cells, IHC is specialized for afferent, and OHC for efferent, communication.

potential. Now, let me emphasize a couple of items. The two types of sensory cells, inner and outer hair cells, are very different in morphologic appearance. Outer hair cells are fairly stereotyped. They are slender, cylindric cells about the same diameter through the cochlea, but the length is graded from one end of the cochlea to the other with a ratio of about 4 to 1, which is a very large change. The shortest cell is about 20 μm, the longest maybe as large as 90 to 100 μm. Inner hair cells have structures on their basolateral side that are the typical morphologic signatures of chemical synapses. There are also a large number of postsynaptic neuronal elements associated with this region of inner hair cells. So, what inner hair cells obviously do in response to this changing receptor potential is liberate chemical transmitters that then begin a process of auditory signal transmission in the afferent fibers of the auditory nerve. Outer hair cells, as I demonstrate below, have very few afferent fibers, but they have a huge descending or efferent innervation. Outer hair cells probably have a motor function, which in Fig 1 is signified by the voltage-to-movement conversion process, and they probably somehow influence their mechanical environment.

Let's examine this further. First of all, consider what is similar about the two hair cells, and what is different. When one records intracellularly from an anesthetized animal, one is able to measure the responses as voltage changes to stimuli from both inner hair cells and outer hair cells. The data shown in Fig 2 are the electrical responses of these two types of

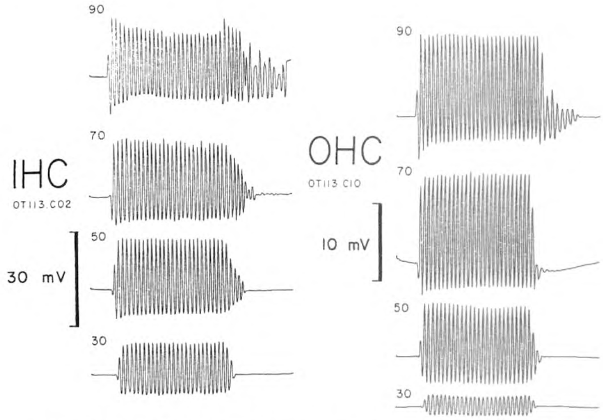


Fig 2. Receptor potential waveforms from IHC and OHC recorded from same organ of Corti at different sound levels (SPL shown as numbers by plots). Responses to 1-kHz tone bursts. (Plots from Figures 5 and 6 in Dallos, J Neurosci 1995;5:1591-608.)

cells at different sound levels from the same cochlea. The main result is extremely simple. Both of these cells generate electrical responses, receptor potentials, graded in magnitude with the signal, reflecting the waveform of the signal. These responses can be very large, as much as 30 to 40 mV. The message is that both cells respond pretty much the same. So the two types of receptor cells, inner hair cells and outer hair cells, produce electrical responses in a very similar fashion — at least in our hands they do.

The latter caveat refers to an important point. There are two ways of making hair cell electrical measurements in the live animal. To do so you have to open up the cochlea, enter it with microelectrodes, and impale a hair cell and record from it for several minutes. But there are two ways of doing it. The first approach was produced by Ian Russell and Pete Sellick, who opened the scala tympani in the very basal, high-frequency end of the cochlea and put electrodes through the basilar membrane into either inner or outer hair cells. Our approach is to open the lateral, bony wall of the cochlea and go in parallel with the top of the organ of Corti, into either outer or inner hair cells (Fig 3). This lateral approach can be used anywhere in the cochlea. Therefore, it is suitable for both the high-frequency and low-frequency ends of the cochlea.

I would like to be able to say that what I am telling you is absolutely true. Most things that I will tell you are probably close to being true, but in science there are stages in the development of knowledge, and until everything has been repeated three times and everybody agrees, there is controversy. The only difference that we can see with the two different approaches from the high-frequency end and the low-frequency end of the cochlea pertains to outer hair

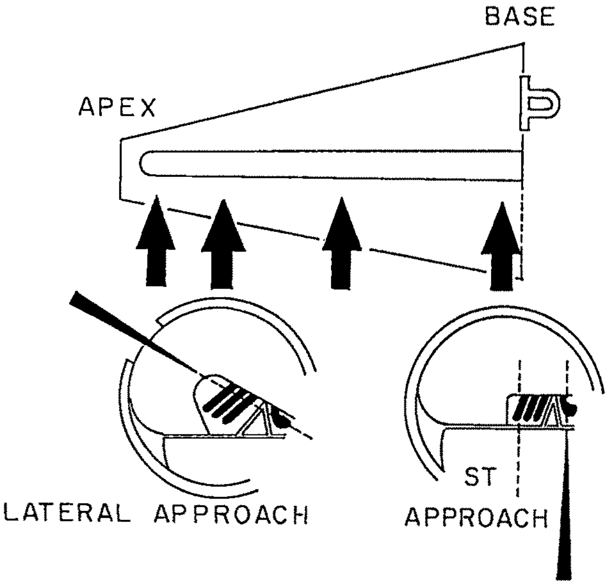


Fig 3. Drawing of two approaches to recording from cochlear hair cells in vivo. Scala tympani (ST) method is useful for recording from basal (high-frequency) region, while lateral approach can be used to record from any turn. It has been used to record from turns 2, 3, and 4 of guinea pig cochlea. (Figure 2 from Dallos. In: Corey DP, Roper SD, eds. Sensory transduction. New York, NY: Rockefeller University Press, 1992:375.)

cells. Inner hair cells produce exactly the same type of response. There is no argument there. Outer hair cells pretty much produce the same type of response that follows the stimulus waveform from instant to instant. Notice in Fig 2 that these waveforms are highly asymmetric, being much larger up than down. That is called the DC component of the response, which is a distortion component, but which is very important in the functioning of the ear. Outer hair cells in the low-frequency region of the cochlea generate very large such DC components, and outer hair cells in the high-frequency region of the cochlea do not, until you get up to an extremely high sound pressure level. So that is one controversial, interesting major difference between outer hair cells in the basal end of the cochlea and the apical end of the cochlea or, if you will, in England and in Evanston. So it remains to be seen.

I said at the beginning that the receptor ends of the two types of hair cells are very similar in the production of receptor potential. There is, however, one extraordinary, profound difference between the two types of cells that was originally shown by Heinrich Spoendlin in the late 1960s. What he found was that the innervation of the two types of cells is completely asymmetric. Inner hair cells receive 90% to 95% of the afferent nerve fibers, and outer hair cells only about 5%. If we knew nothing more about the auditory system, we would immediately venture that inner hair cells are the true sensory receptors of the ear, because they are the ones that convey virtually all auditory information to the brain. Let me mention in passing that there must be 10,000 papers in the literature describing responses from the auditory nerve. Every one of those 10,000 describes the responses that are measured in nerve fibers coming from inner hair cells.

We have absolutely no idea what, if any, informa-

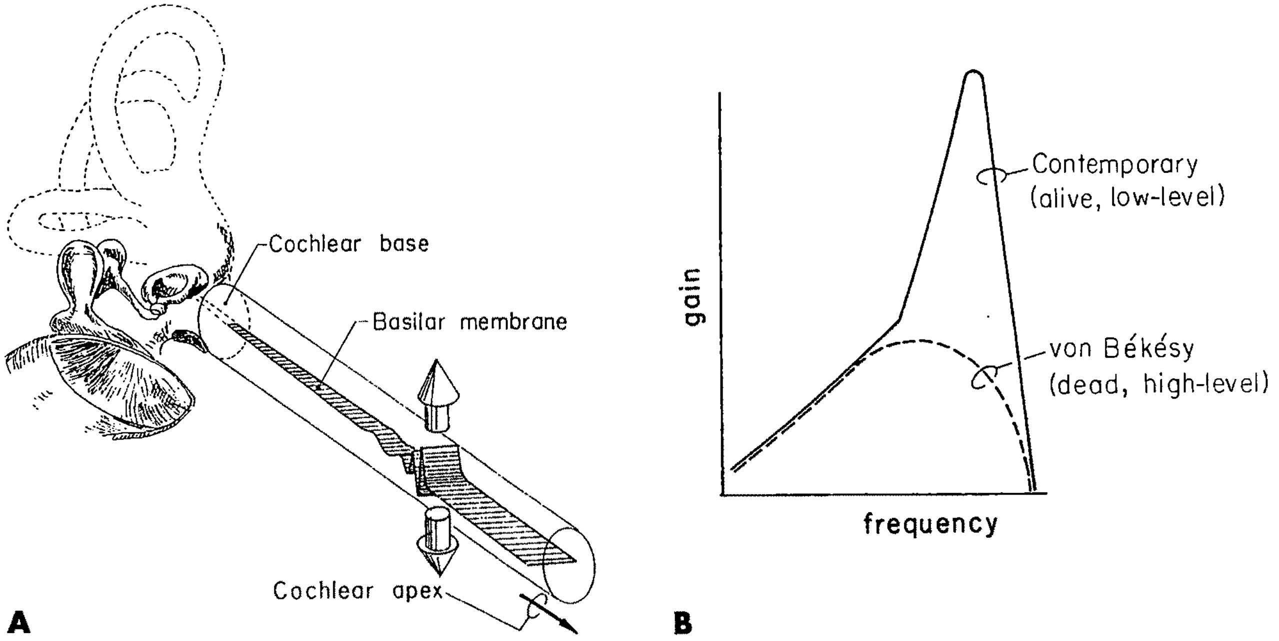

Cochlear base
Basilar membrane
Cochlear apex
A
gain
frequency
Contemporary (alive, low-level)
von Békésy (dead, high-level)
B

Fig 4. A) Drawing of cochlea shown unrolled with basilar membrane as ribbon. "Snapshot" of basilar membrane's displacement pattern is shown for single-frequency stimulus. Three-dimensional arrows indicate location of measuring displacement. B) Gain of displacement (basilar membrane displacement divided by stapes displacement) measured at location of arrows.

tion is transmitted to the brain from those fibers coming from outer hair cells. So, inner hair cells are the true sensory receptors, and of course the most interesting question over the past 20 years — at least to me — has been what outer hair cells do. And that is what I am going to discuss for the remainder of this paper.

The clues to what outer hair cells might do occurred fairly early in the game, in the 1970s. Consider the basilar membrane, and let's assume that I measure the amplitude of its vibration as a function of frequency when the input is kept constant. What we know about such a measurement is that the gain of this response vis-à-vis the input can be described by the so-called tuning curve. That is, at any given location, as frequency changes, there will be a point where you have a maximum response, and at other frequencies you have a lesser response. This is one of von Békésy's major findings and his crowning glory — the description of the traveling wave. This spatiotemporal distortion pattern on the basilar membrane analyzes incoming sounds according to their spectral components, so that high frequencies are maximally exciting the basal region of the cochlea, and low frequencies, the apical region. Von Békésy made his measurements at very high levels in cadavers, and he found relatively poor tuning (Fig 4).

Contemporary measurements from a number of laboratories indicate that when you measure basilar membrane responses in a live animal at low sound levels, you have extremely sharp tuning. And as you go to higher and higher levels in sound, the tuning deteriorates. This poor tuning, this high-level dead-cochlea tuning, is the effect of the physical structure of the cochlea and the basilar membrane. It is a very simple physical process. But what we see in the live cochlea is that this physical process is somehow amplified, boosted, especially at lower levels, and this difference between the high-level and low-level gain is what we now describe as the cochlear amplification process that occurs in the live mammal. It is the process that gives the auditory system its extraordinary sensitivity and frequency-resolving capability.

So, this is the process that seems to deteriorate when outer hair cells are destroyed or when outer hair cells are interfered with. When outer hair cells, for example, are incapacitated by some means, then this extraordinarily high-gain, fine, sharp tuning deteriorates into the low-gain, dead-cochlea type of tuning. The outer hair cells are somehow responsible for this difference between the two types of response. The systems engineer would describe the process of transduction schematically: 1) the passive mechanics of the cochlea feed into the outer hair cells, 2) the outer hair cells produce a receptor potential, 3) the receptor potential powers a motor in the outer hair cell that 4) feeds back energy that 5) boosts the response to produce the active mechanics, which is 6) sensed by the inner hair cell and 7) delivered to the brain by the auditory nerve fibers. Another way of describing it, and probably a more transparent way of talking about it, is this: the basilar membrane is moving up and down, and the hair cells are stimulated by the relative motion between the tectorial membrane and the organ of Corti. The cilia are bent, and receptor potentials are generated. In response to that, outer hair cells change their shape and feed mechanical energy back onto this vibrating substance on which they are sitting, thereby changing the input into the inner hair cell, which then produces the input to the brain. That is the schema.

In 1983, Bill Brownell discovered that isolated outer hair cells change their length when their electrical environment changes. That gave us the step that was required to know how outer hair cells may influence their environment. What he found was the following. When you have an outer hair cell isolated and you depolarize this cell, making it more positive inside, then it becomes shorter and fatter. When you hyperpolarize the cell, it becomes longer and skinnier. In other words, there is a real shape change to these cells upon electrical stimulation. This shape change is not trivial; it can be as large as 5% of the length of the cell. If you take a 100-μm-long apical cell, it can maximally contract by close to 5 μm, which is a huge biologic change. So, this electrically driven shape change may be the means whereby outer hair cells affect their environment mechanically.

The remainder of this presentation will be a description of and some questions about such shape changes: how they might come about, what their properties are, what drives them, and so forth. These shape changes are extremely unusual. Ordinary cellular motors that we know about in biology are dependent on enzymatic processes, which in turn depend upon the presence of adenosine triphosphate (ATP) and calcium. So, for example, in muscle contraction, myosin working on actin is an enzymatic process. Kinesin working on microtubules is an enzymatic process. It requires local energy consumption in the form of ATP, and it requires the cofactor calcium to be present. The fast outer hair cell motility requires neither ATP nor calcium. So, you immediately know that it is a different beast than what we are used to in biology in terms of biologic motors.

Various types of experiments have indicated that the outer hair cell motor functions through a very

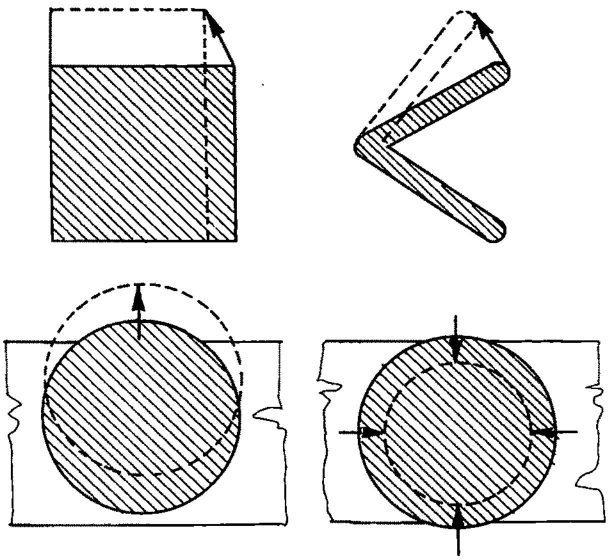


Fig 5. Possible changes in configuration of motor molecule located in OHC membrane. Top two possibilities depict anisotropic changes in configuration with arrows indicating displacement vector. Bottom two show isotropic change with molecule moving in and out of plane of membrane (left) or changing its volume (right).

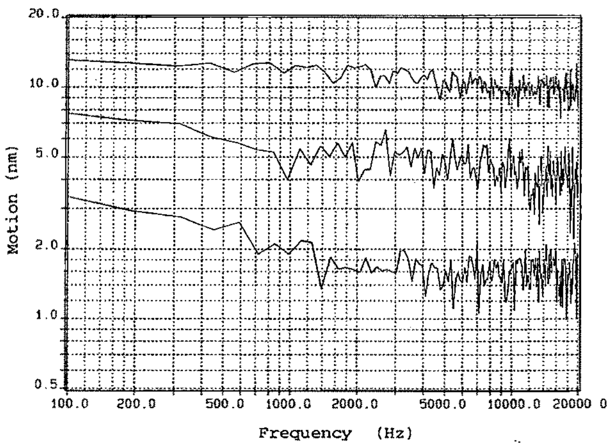


Fig 6. Three examples of OHC motility amplitude measured in partitioning microchamber as function of frequency of command voltage. Note that at high frequencies, response is asymptotic to constant. (Unpublished data from B. N. Evans and P. Dallos.)

large number of independent displacement motors distributed along the length of the outer hair cell. There are probably millions of such molecular motors distributed along the cellular envelope. These motors are driven by local voltage changes, ie, by the change in the membrane potential of the cell. Moreover, the actions of such elementary motors sum, so that you get a total contraction-elongation cycle upon electrical stimulation. I think most people working in the field will agree with this.

So, where are those motors, and what is their nature? In an electron microscope picture of the perimeter of an outer hair cell, right next to the cell membrane, there are some very interesting structures. There are a relatively large number of mitochondria in that region, and systems of what appear to be smooth endoplasmic reticulum forming concentric layers. If you take slices of an outer hair cell, then what you see here is layer upon layer of such subsurface cisterns or endoplasmic reticulum, and between the outermost of such layers and the cell membrane, there is an extremely elaborate cortical structure. The cell membrane is studded with a variety of proteins. It appears from freeze fracture studies, first from Gulley and Reese, and from others later on, that the outer hair cell is in fact quite unique, in that, according to Andy Forge, as much as 75% of its surface is covered by protein, which is incredibly high compared to all other types of cell. Between the proteins in the cell membrane and the subsurface cisterns is an organized network of actin filaments, running essentially like a helix along the length of the cell, and these actin filaments are probably cross-linked by spectrin links. The actin filaments are attached, conceivably, to the proteins, but certainly to the cell membrane by some pillar structures. These form a rather unique, extremely organized network, which might be related to the outer hair cell motor response. It doesn't take a great deal of biophysics to realize that the sensor for whatever the motor is must be in the membrane, because if it is a transmembrane voltage that drives it, then you have to have an electrical potential appearing across the sensor. So, the sensor has to be in one of these proteins. The most parsimonious assumption — and there is some experimental evidence to support it — is that the sensor and the membrane are parts of the same protein. So, we assume that this conglomeration of protein molecules in the membrane is, in fact, the sensor-motor structure. And there are, of course, various ways of thinking about how such a motor — a molecular motor — might produce a displacement. This is a very interesting issue and nontrivial.

The most commonly assumed form of the motor action is that the protein molecules, under voltage control, move in and out of the membrane and thereby change the surface area of the membrane, which would then translate to a length change (Fig 5).

A second possibility, of course, is that the protein itself somehow contracts and expands. Another possibility is that the change is not symmetric and that the motor moves more, displaces more in one direction or in another, which is equivalent to saying that maybe just as in a rhodopsin molecule, you have some kind of a conformational change that changes the angle of orientation of the motor. We don't know the answer yet, but these are all possibilities. Some interesting experiments have asked whether this motor is isotropic or anisotropic. Is it symmetric, or is it directed? These will tell us a great deal about the nature of this protein. So, the point is that if you have millions of such proteins, which is the estimate per hair cell, which then change their conformation under voltage control — if there are sufficient numbers of them that change the same way — then that will add up to an elongation or a contraction. At the same time, it will change the diameter of the cell as well.

This cellular elongation-contraction cycle is extremely asymmetric. Our experiments indicate that the principal motion is a contraction of the cell upon depolarization. The response can be described as a second-order Boltzmann process, which indicates that the motor is probably akin to some sort of a channel protein that is probabilistically responding to voltage changes. That is the easiest way of describing the entire operation. If we look at the longitudinal change in response to a sine wave voltage, there is asymmetry in the following of the voltage by the length change, and at the same time, the following of the change in the diameter of the cell. So, the cell is alternately getting longer and skinnier and then fatter and shorter. The point is that it is a concerted change of the dimension of the cell, as if the cell were at constant volume.

How fast can the cell change shape? One can put an isolated living outer hair cell into a suction chamber, and balance its electrical properties so that the cell membrane's electrical influence upon the motor is essentially eliminated. In such an experiment one can examine the capability at the motor itself by divorcing it from the influence of the electrical properties of the cell membrane, which is important, as we will see in a few minutes. If you do that, then you can measure the magnitude of displacement of the cell as a function of input frequency, up to as high as our equipment is capable of doing.

Notice that the response is fairly flat (Fig 6). Frequency is on the abscissa, and displacement in nanometers on the ordinate. For any of these curves, there is virtually no change up to about 24 kHz, which is the limit of our equipment. Now, this means something very important: it means that the motor itself, the molecule itself, is capable of conformational changes, at least as fast as 40 microseconds, and probably much faster.

The point is that this biologic motor is capable of extremely rapid responses, orders of magnitude faster than any other biologic motor known to mankind. The final point is that you can show that it is not only when you artificially change the voltage across the cell membrane that you get this contraction-elongation cycle, but that it occurs naturally. In an experiment we did with Burt Evans, in which we put the cell into this chamber so we could deliver a voltage across it, we used a fluid jet to move the ciliary bundle, which is the normal stimulation in mammals, and we measured the displacement of the far end of the cell. We found a following response to the sinusoidal ciliary displacement. When you increase the membrane potential, it facilitates the response; you get a much larger response. Thus, we can assume that the motion of the ciliary bundle in vivo produces the same hair cell elongation-contraction cycle. That is comforting, because that means that now we can really think about this as the substrate of the cochlear amplification process.

Now let me spend the remaining few minutes throwing a couple of monkey wrenches into this lovely machinery that I have described for you. Earlier I was bragging about the wonderfully broad frequency response of the motors, and I said that we can measure it up to 24 kHz, which is the limit of our equipment. I said that we can do that because we eliminated the influence of the cell membrane as an electrical circuit. Well, in vivo you can't do that, because every cell in the body has a membrane that contains capacitance so it is able to act as an insulator, and then, of course, it has some resistance due to the various channels that are in the membrane. This is what we call an RC (resistance-capacitance) circuit that functions as a low-pass filter. In other words, when you deliver a receptor current into the cell by the deflection of the cilia and thereby produce a voltage gradient across the ciliary membrane, that will appear across this membrane filter. And since that is the voltage that drives the motors, you immediately see that you have a problem. If you made computations on the basis of available data, then you find that this corner frequency where the filter starts to cut off is, at best, 1,000 Hz and probably much, much lower, which means that when you get up to 20 to 30 kHz you have very little voltage left to drive the motor.

What happens? The answer is that I don't know. But we have a few ideas, and let me share those with you. These are preliminary ideas, and I really don't have the whole picture completed.

Imagine a circuit diagram of the outer hair cells showing their apical impedance, apical membrane, and basolateral membrane impedance. Some of the outer hair cells are active, in that they are being stimulated, and some are inactive, because they are receiving very little stimulus. When one analyzes a circuit of this sort, one finds a remarkable result: when you measure the voltage drop as a function of

P26 I17

frequency on an active outer hair cell, it cuts off very rapidly. When you measure it across a passive outer hair cell, it cuts off much less. Now let me say that again. This picture of the active portion fundamentally conforms to our original argument that there is a membrane capacitance, so you have a low-pass filter. The problem is that when you put an outer hair cell into the context of many more outer hair cells in a complex circuit, then the active outer hair cells cut off even faster than a simple low-pass filter, which makes life much worse than everybody assumed before. The interesting part is that the passive outer hair cell behaves much better for very complex electrical reasons. So, it would be at least conceivable that the traveling wave would activate cells above a particular excitation magnitude. The cells below that magnitude would be "passive." The passive cells, away from the peak of the traveling wave, that will be excited more by electrical signals from their neighboring cells will produce the elongation-contraction cycle, and they will be the ones that then feed back energy to the traveling wave.

Now, the cognoscenti among you will appreciate this, because all the modelers say that the active process has to be basal from the peak of the traveling wave, and so this at least gives you a plausible mechanism for that operation. Outer hair cells that are apical from the traveling wave, which are also stimulated electrically, will not couple energy back to the basilar membrane, because they are above the cutoff frequency of the basilar membrane. So, all I am giving you is one possible partial rescue of the scheme, which is not a very convincing one, I must admit. But if something of this sort does not work, then this entire scheme of amplification will not work at high frequencies, and that is where we in fact need such amplification, particularly if you consider small rodents that are operating up to 60 to 70 kHz in their auditory range. Presumably, they have a cochlear amplifier of some sort, and it is very difficult to conceive of if you don't produce some such scheme of how they might function.

The point of all this is that we have a need for amplification, we know that it is there, we know that outer hair cells are involved, and we know that outer hair cells are motile and respond to voltage; but we have a fundamental problem that has not been entirely solved of how this entire scheme might operate at very high frequencies, and so this field is active, no pun intended, in looking for answers. They should be forthcoming in the next few years.

The other question, of course, will be the identification of the molecular motor: what it is, what sort of a molecule it is, what its sequence is, and so forth. I assume that some of that will be done here at Bloedel, and I look forward to reading it in the literature.

Ann Otol Rhinol Laryngol 106:1997

FUNCTIONAL ASYMMETRIES IN THE AUDITORY SYSTEM

JAMES JERGER, PHD
HOUSTON, TEXAS

This paper describes interaural differences in a variety of listening tasks. We summarize both behavioral and electrophysiologic evidence that performance, in persons with both normal and impaired hearing, differs according to which ear is stimulated. The effect extends over the entire age range, but is especially evident in children and elderly persons. Results are presented in three areas: 1) cued listening, 2) dichotic words and sentences, and 3) temporal resolution. Some possible clinical implications of functional asymmetries are discussed.

KEY WORDS — absolute pitch, aging, auditory evoked potentials, corpus callosum, dichotic listening, event-related potentials, mismatched negativity, N400, P300, semantic incongruity, temporal resolution.

INTRODUCTION

The data reported in this paper were gathered over a period of several years in the auditory research laboratories of the Baylor College of Medicine. This program of research arose as the result of incidental findings from other work,[1,2] mostly concerned with the problems that elderly persons face in using hearing aids. Data suggested that the separate testing of the two ears, neglected in much previous research on auditory function, especially in the area of auditory event–related potentials, might yield some important insights. We set out, therefore, to compare and contrast the two ears on a variety of listening tests across a wide range of ages. A task involving cued listening in a sound field was the initial impetus for much of the later work.

CUED LISTENING

Our laboratory, like many others, has long been concerned with the problems of elderly hearing aid users, especially the difficulties that they report when they try to follow a conversation in a background of competing speech or noise. About 5 years ago we set out to recreate, in the laboratory, this kind of listening task.[3] Figure 1 shows the arrangement of apparatus. The listener is seated between two loudspeakers. One loudspeaker delivers continuous discourse, a detective story written in the first person (eg, "I got up, I strapped on my gun, I lit a cigarette, I reached for a can of beer"). The opposite loudspeaker delivers the same story, but delayed by 60 seconds. The listener hears the same talker, reading the same material, but a different part of the story. A third loudspeaker, mounted directly above the listener, delivers multitalker babble. A signal light cues the listener to attend either to the right or to the left speaker. The cued

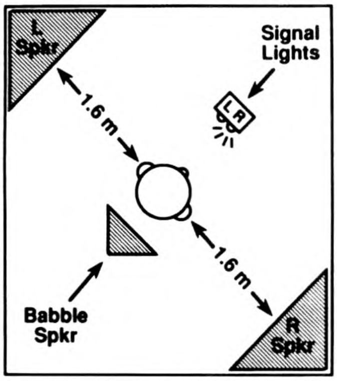


Fig 1. Physical arrangement of loudspeakers (Spkr) for cued-listening task. LR — left and right.

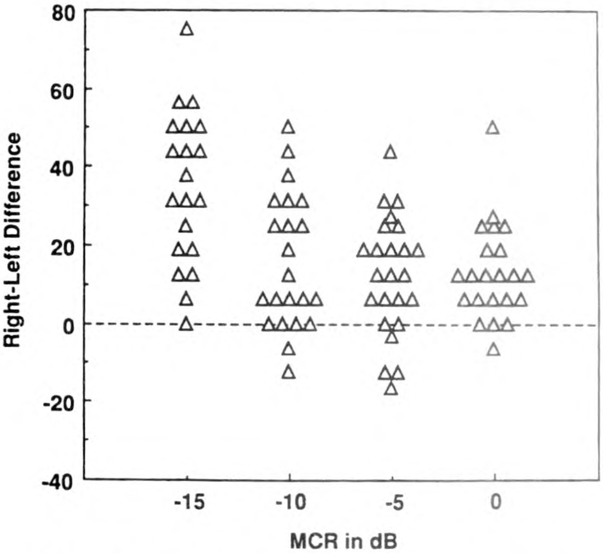


Fig 2. Scatter plot showing individual right-left differences of 28 elderly persons with presbyacusis at four message-to-competition ratios (MCR).

From the Department of Otorhinolaryngology and Communicative Sciences, Baylor College of Medicine, Houston, Texas. Supported by The Albert and Ethel Herzstein Foundation and the National Institute on Aging (grant AG-08958).

CORRESPONDENCE — James Jerger, PhD, Dept of Otorhinolaryngology and Communicative Sciences, Baylor College of Medicine, 11922 Taylorcrest Rd, Houston, TX 77024-4300.

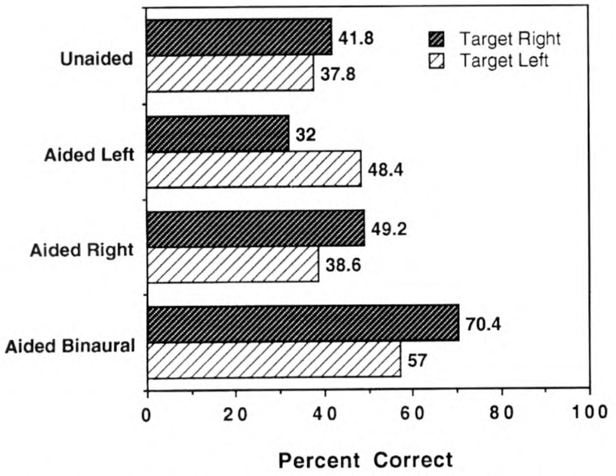


Fig 3. Mean aided and unaided results for right and left direction targets in 10 elderly binaural hearing aid users.

loudspeaker is randomly varied, over 10 successive blocks of 10 trials each, with the constraint that each side is cued on exactly five blocks. The target response is the personal pronoun "I." The listener must respond to each "I" from the target speaker and ignore "I"s from the nontarget speaker. We called this the "cued-listening task" and designed it as a method for evaluating the performance of elderly hearing aid users.

Because of the physical arrangement, this is a quasidichotic listening task, in which uncorrelated speech signals reach the two ears simultaneously. We were not surprised, therefore, to find a small right-sided performance advantage (about 5%) in 19 young persons with normal hearing in the age range from 21 to 30 years. We were surprised, however, to find a relatively larger right-sided advantage, or left-sided disadvantage, in elderly persons, in spite of the fact that hearing sensitivity loss was equal in the two ears.

Figure 2 shows the distribution of the right-left difference in 28 elderly persons, in the age range from 52 to 84 years, at four target-to-babble ratios. These differences average about 20% and range as high as 60%.

In a later study[4] we used the cued-listening task to evaluate binaural hearing aid performance in 10 elderly presbyacusics in the age range from 48 to 88 years. Subjects were tested in four conditions: unaided, right ear aided, left ear aided, and both ears aided. Figure 3 summarizes mean group accuracy scores by amplification condition and by target direction. In the unaided condition, there was a 4% advantage when the target came from the right side. In the two monaurally aided conditions, the expected differences occurred. When the left ear was aided, performance was better when the target came from the left side. When the right ear was aided, performance was better for right-sided targets. In the binaural condition, however, where both ears were aided, there was a significant 14% difference in favor of right-sided targets.

DICHOTIC WORDS AND SENTENCES

These relatively large interaural asymmetries, both unaided and aided, stimulated our interest in dichotic listening in the elderly.[5,6] What happens to the normally small right ear advantage for verbal tasks as age increases? Figure 4A shows the mean scores for right and left ears of 384 patients ranging in age from 10 to 94 years on the dichotic sentence identification (DSI) test.[7] These scores are based on a free-report paradigm, presented under earphones, in which the listener reports both sentences in any order. Note the systematic divergence of the two ears with increasing age. In the age group greater than 80 years, the difference is about 40%. To what extent is this increas-

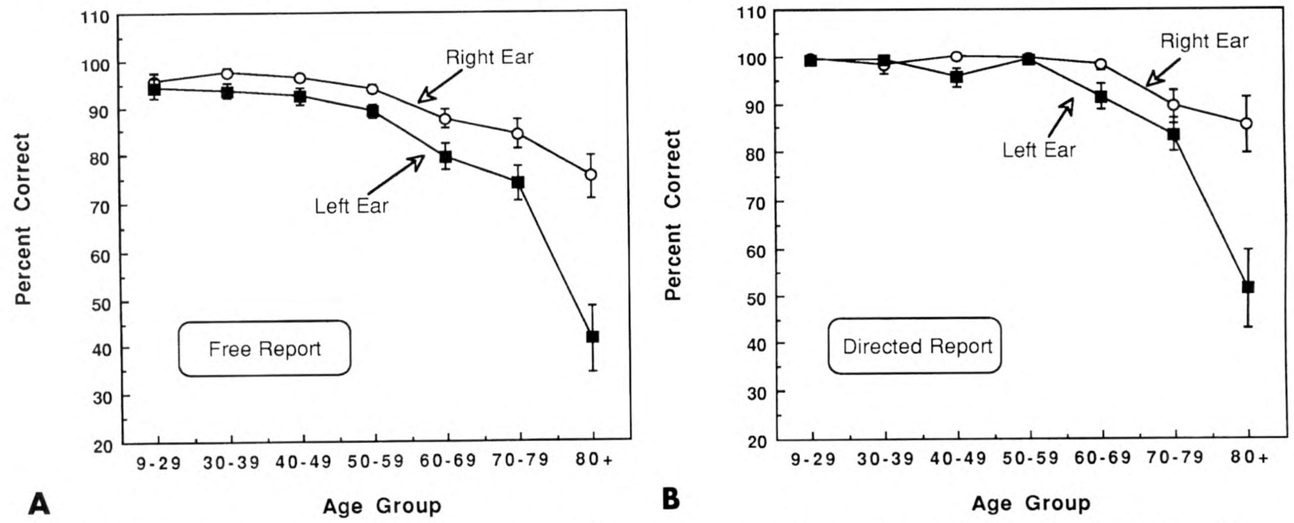


Fig 4. Effect of age on dichotic sentence identification (DSI) test performance. Means and standard errors of right and left ear data. A) Free report mode. B) Directed report mode.

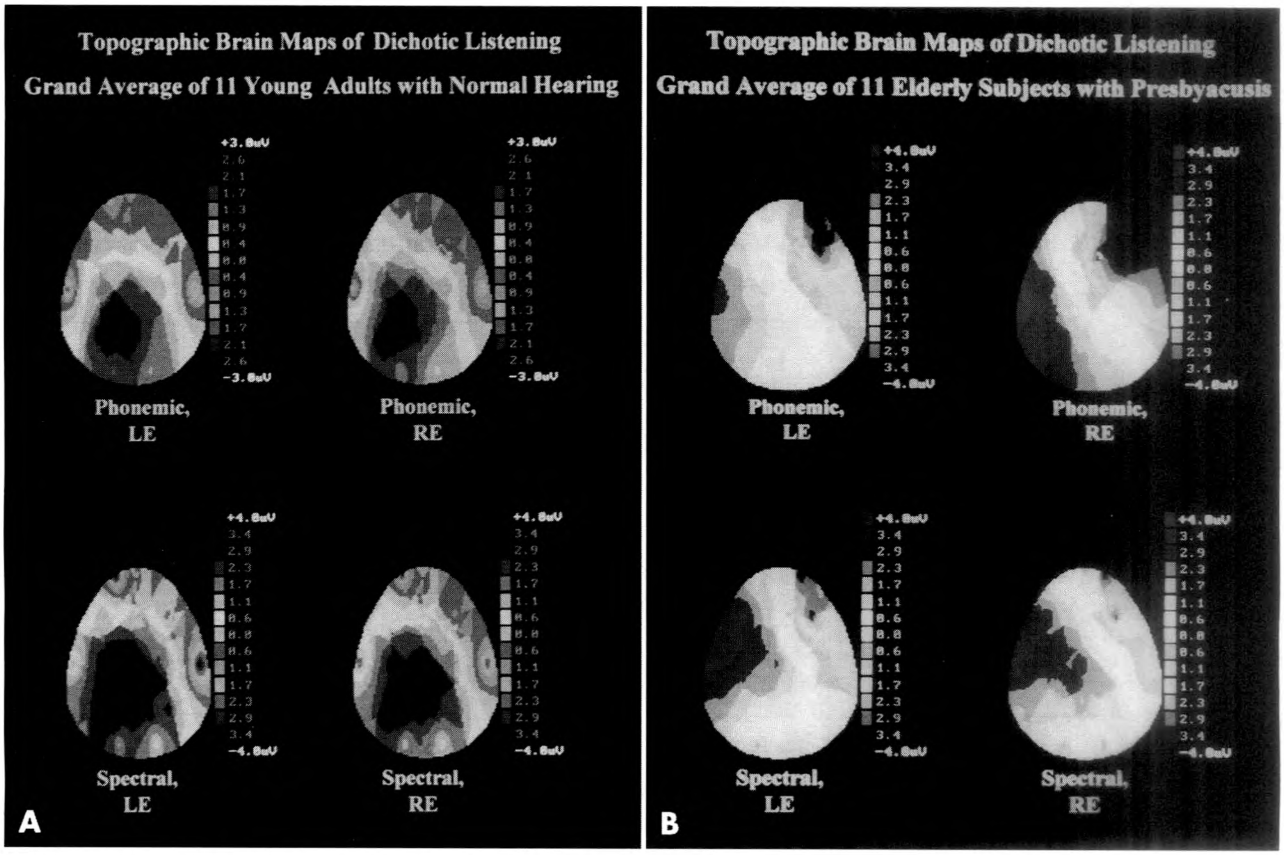

Topographic Brain Maps of Dichotic Listening
Grand Average of 11 Young Adults with Normal Hearing
+3.0uV
-3.0uV
Phonemic, LE
Phonemic, RE
+4.0uV
-4.0uV
Spectral, LE
Spectral, RE
A
Topographic Brain Maps of Dichotic Listening
Grand Average of 11 Elderly Subjects with Presbyacusis
+4.0uV
-4.0uV
Phonemic, LE
Phonemic, RE
Spectral, LE
Spectral, RE
B

Fig 5. Topographic brain maps at peak of P300 waveform for verbal and nonverbal tasks. Darkest areas reflect greatest positivity. LE — left ear, RE — right ear. A) Grand average of 11 young adults with normal hearing. B) Grand average of 11 elderly persons with presbyacusis.

ing right ear advantage, or left ear disadvantage, the result of an interaction between the memory demands of the free-report paradigm and the memory loss often associated with aging? Figure 4B shows mean scores for the same subjects in a directed-report paradigm in which only one ear is reported. Here, where the memory load is attenuated, the effect is slightly smaller, but the same general pattern persists.

In view of these marked, seemingly age-related effects, we developed evoked potential indices of interaural asymmetry[8] based on the P300 event-related potential. We developed two dichotic tasks: one based on verbal processing and one based on nonverbal processing. Both tasks are based on the simultaneous presentation of phonemically balanced (PB) words to the two ears in a conventional "oddball" paradigm. The frequent event, a randomly selected pair of PB words spoken by a male talker, occurs on 70% of trials. For the verbal task, the listener monitors the word pairs for a predefined target word (the oddball event) containing the phoneme "ook" (eg, "look," "took," "cook," "book," etc). For the nonverbal task, the listener monitors the same words, but for a predefined target voice (ie, a word spoken by a female talker). In both tasks, the rare event occurs on 30% of trials: 15% to the right ear and 15% to the left ear. Electroencephalography was recorded from 22 scalp electrodes affixed according to the international 10-20 system.[9] Responses to right ear targets and to left ear targets were separately averaged. Waveforms to targets were subtracted from waveforms to nontargets to define the P300 response at each electrode. Topographic brain maps (TBMs) were constructed by interpolating voltages between adjacent electrodes and assigning gradations of blackness to voltages according to a standardized scheme.

Figure 5A illustrates the TBMs for right and left ears on the verbal and nonverbal tasks, grand-averaged over data from 11 young adults in the age range from 18 to 32 years. Each TBM represents the distribution of positivity over the scalp at the peak of the P300 waveform. The darkest areas reflect the greatest positivity. Results in the four conditions are difficult to differentiate. The area of maximum positivity is slightly larger for the right ear on the verbal task, and slightly larger for the left ear on the nonverbal task, but the differences between ears are not easily discerned. Figure 5B shows analogous TBMs for 11 elderly persons in the age range from 73 to 84 years with bilaterally symmetric presbyacusic hearing im-

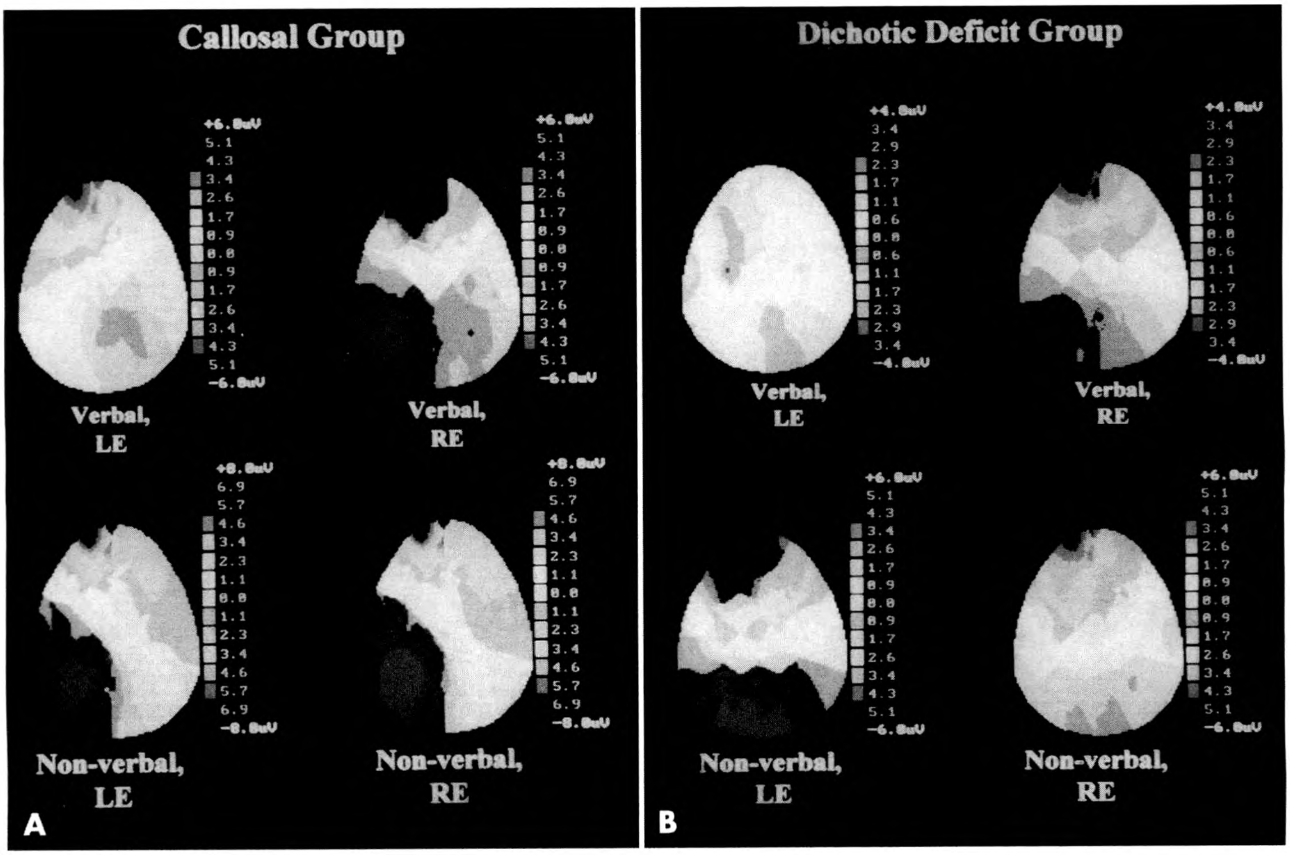


Fig 6. Topographic brain maps at peak of P300 waveform for verbal and nonverbal tasks. Darkest areas reflect greatest positivity. A) Grand average of 6 patients with lesions of corpus callosum. B) Grand average of 4 presbyacusics with left ear dichotic deficit on DSI test.

pairment. There are two differences between the TBMs of the young and elderly subjects. First, the right-left difference on the verbal task is larger in the elderly group. Second, the area of maximum positivity, for both the verbal and nonverbal tasks, has shifted from symmetry around the midsagittal plane to the left posterior quadrant. Figure 6A shows the same four TBMs grand-averaged over 6 young adults, in the age range from 10 to 56 years, with known lesions of the corpus callosum. The same pattern observed in the elderly group with presbyacusis is evident here. The right-left difference in positivity is larger on the verbal task, and the area of maximum positivity has shifted from midline to the left posterior quadrant. Finally, Fig 6B shows the same four TBMs grand-averaged over 4 elderly persons in the age range from 81 to 88 years, with substantial left-sided dichotic deficits as measured behaviorally by the DSI test. We see, here, both the greater response from right ear targets on the verbal task, and the reverse, a greater response from left ear targets on the nonverbal task. Note, also, the shift of maximum positivity to the left posterior quadrant, especially for verbal targets to the right ear.

To what extent are these asymmetries relevant to the general problem of hearing in a background of noise? We present 2 cases showing these asymmetries in patients whose only complaint was difficulty in understanding speech in a noisy background. Figure 7A shows TBMs to verbal and nonverbal tasks in a 20-year-old woman with normal hearing sensitivity but with the familiar complaint that she has great difficulty understanding speech in the presence of background noise or speech competition. Note the ear asymmetry on the verbal task. Figure 7B shows that this asymmetry is not evident when the same target words are presented monotically. Figure 8A shows TBMs in a 64-year-old woman with a mild bilateral sensorineural loss whose only auditory complaint was difficulty understanding speech in the presence of background noise. Note, again, the left ear deficit on the verbal task and the right ear deficit on the nonverbal task. And, again, Fig 8B shows that the asymmetry on the verbal task is not present when the same target words are presented monotically.

TEMPORAL RESOLUTION

We have employed a two-interval, same-different paradigm to evaluate evoked responses to temporal resolution in children, young adults, and elderly persons. Figure 9 shows the temporal relations among the tonal stimuli. It is important to note that these

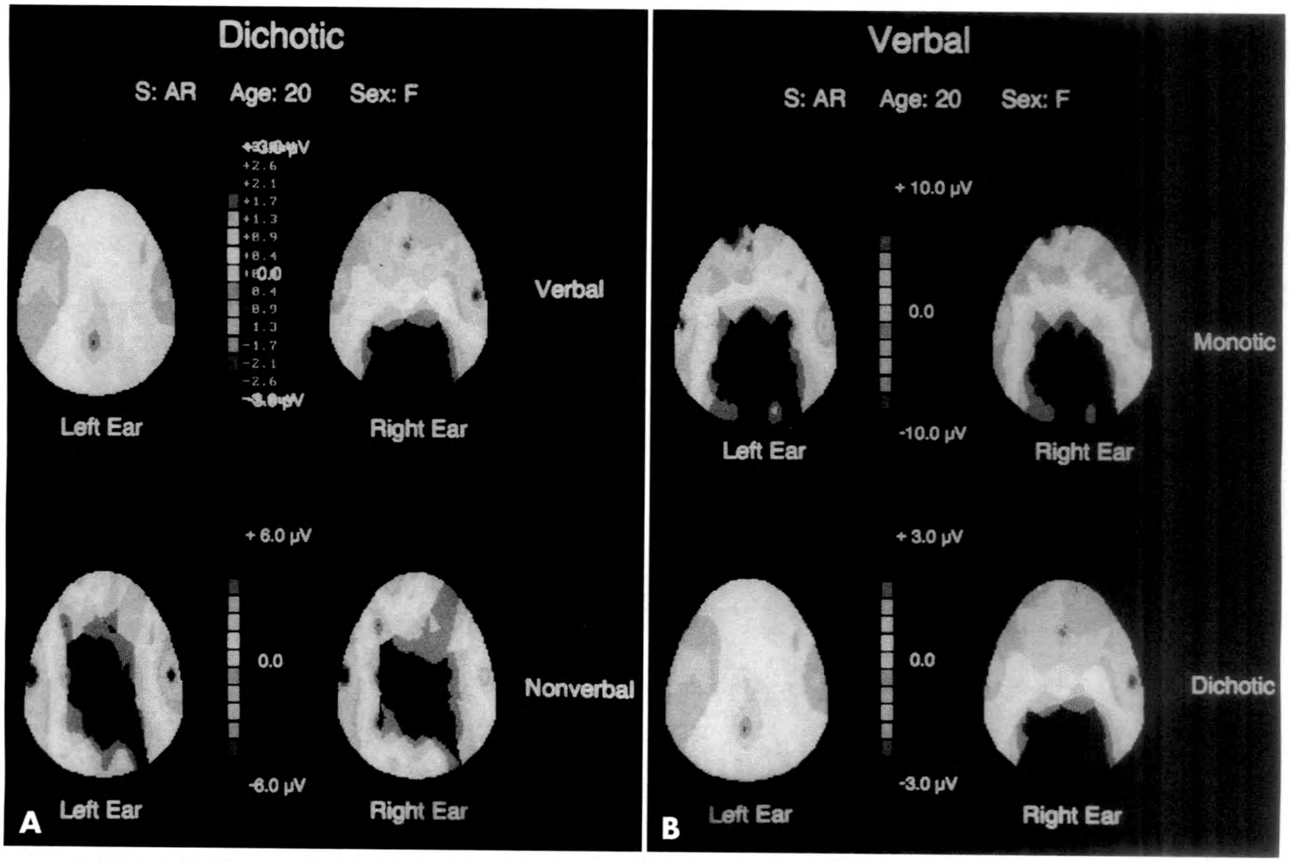


Fig 7. (Subject AR) Topographic brain maps at peak of P300 waveform subject AR, 20-year-old woman with normal hearing who complained of trouble understanding speech in background noise. Darkest areas reflect greatest positivity. A) For verbal and nonverbal tasks. B) For verbal task presented monotically (top) and dichotically (bottom).

target stimuli are always presented monotically, that is, one ear at a time, not dichotically. Within the context of the "oddball" paradigm, we measured the P300 response in three groups of subjects. Figure 10A shows P300 TBMs for right and left ear stimulation in 11 children in the 8- to 12-year age range, 10 young adults in the 20- to 29-year age decade, and 10 elderly persons in the age range from 65 to 90 years. Note that in young adults there is little or no ear difference. In children, however, there is a clear right-left difference in positivity. There is also a smaller right-left difference in the elderly group. In a separate set of 13 children, 8 young adults, and 8 elderly persons, we repeated the entire experiment, but measured the mismatched negativity (MMN) response. Figure 10B shows TBMs for this response in the three new groups. Since the MMN is a processing negativity,[10] rather than a positivity as for the P300, degree of blackness represents negativity rather than positivity. But the overall pattern of Fig 10B is similar to the P300 results of Fig 10A: little interaural difference in young adults, but a distinct right-left difference in children and in elderly persons.

DISCUSSION

Substantial asymmetries in auditory function appear to be more common than we have heretofore suspected. There are at least two important reasons for previous failures to detect these asymmetric phenomena. First, unless you test each ear separately, you will surely miss the effect. Yet systematic interaural comparison, especially in electrophysiologic studies of auditory event–related potentials, has not been a consistent feature of studies of central auditory function. Second, the effects are smallest in young adults. This is the age range of choice in many studies of auditory behavior, but the present data suggest that asymmetric effects may actually be much larger in children and in elderly persons. Is it possible that asymmetry is attenuated by development, is minimal in young adults, and then reappears as auditory function declines with age?

Since many of the asymmetries summarized above are most obvious in elderly persons, it is appropriate to question whether the presence of presbyacusic hearing sensitivity loss plays a role in the observed phenomena. It should be emphasized, therefore, that in all of the group comparisons involving elderly persons, we have controlled for equivalence of hearing sensitivity loss in left and right ears. Furthermore, while the presence of sensorineural loss inevitably

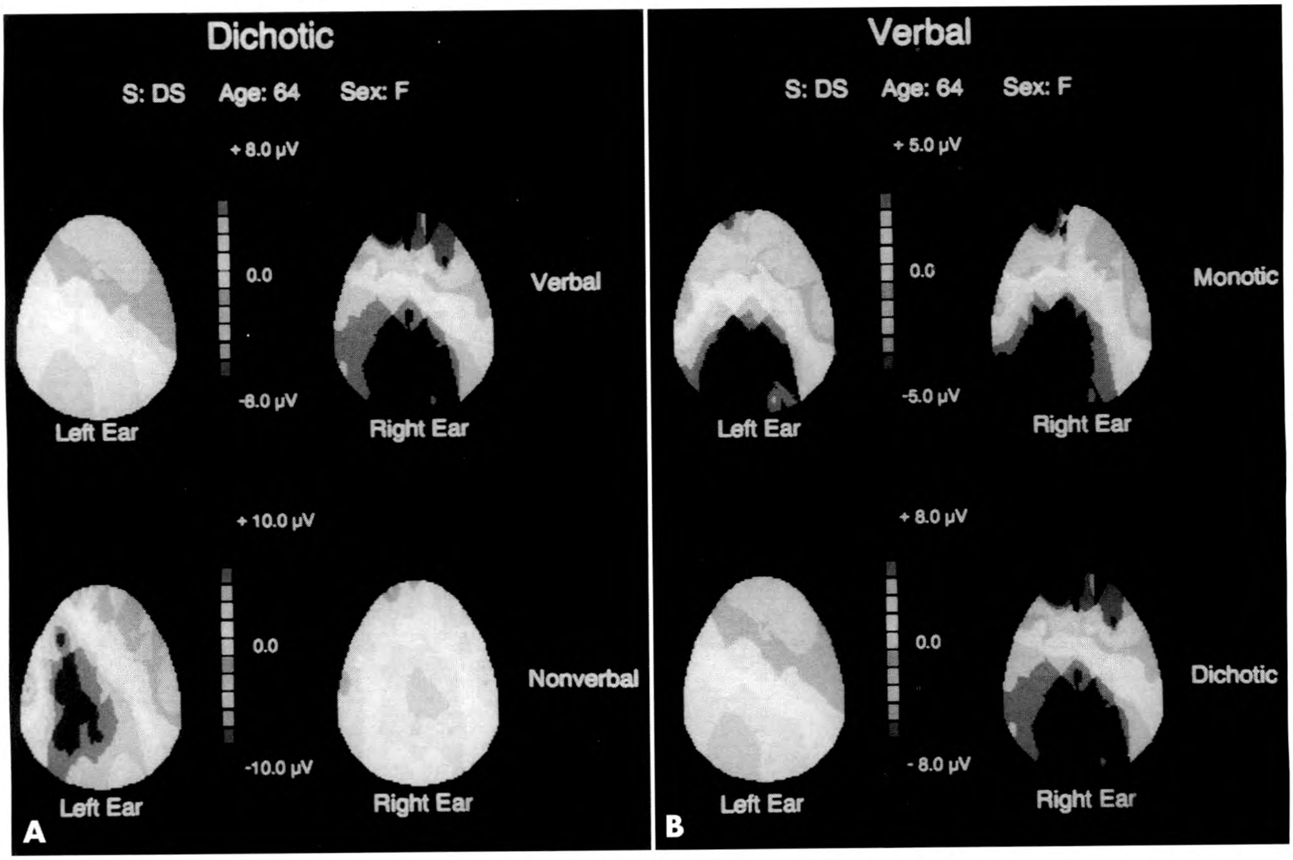


Fig 8. (Subject DS) Topographic brain maps at peak of P300 waveform in subject DS, 64-year-old woman with presbyacusis who complained of trouble understanding speech in background noise. Darkest areas reflect greatest positivity. A) For verbal and nonverbal tasks. B) For verbal task presented monotically (top) and dichotically (bottom).

affects auditory perception in general and speech perception in particular, the interaural asymmetries cannot reasonably be attributed to peripheral factors. In the case of dichotic listening, for example, we have shown that while left ear performance is poorer for the verbal task, right ear performance is poorer for the nonverbal task. Such reversals implicate central rather than peripheral mechanisms.

How can we explain an apparently age-related decline in left ear performance on a verbal task and right ear performance on a nonverbal task? In the case

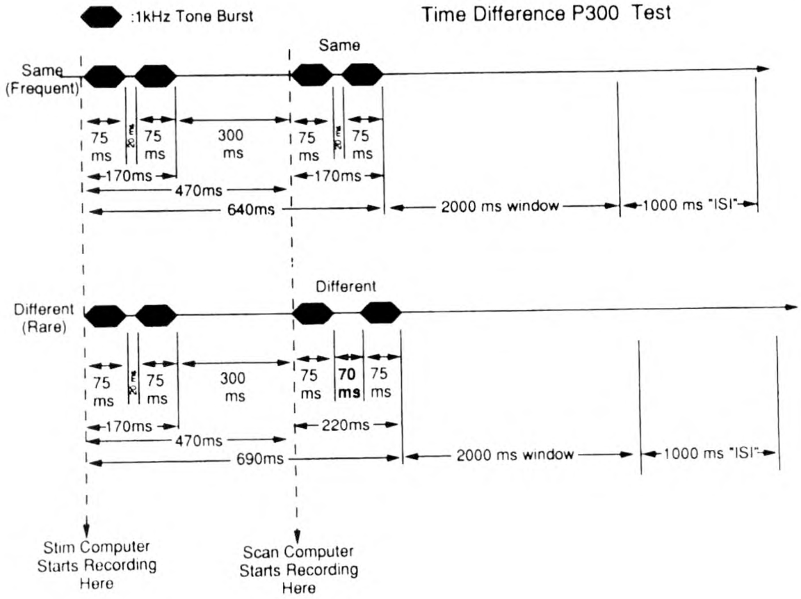


Fig 9. Paradigm for measurement of temporal resolution. ISI — interstimulus interval.

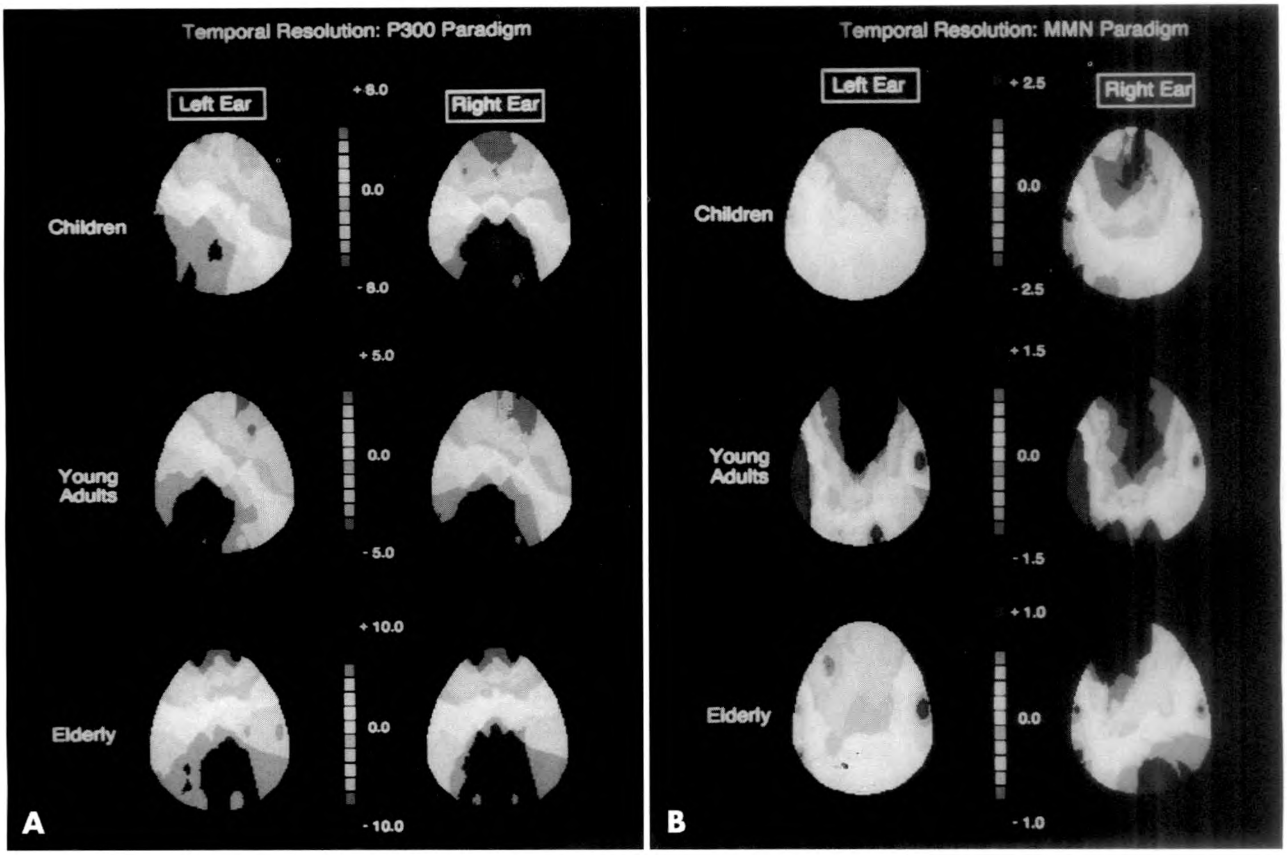


Fig 10. Topographic brain maps for temporal resolution measured separately in right and left ears of three groups: children, young adults, and elderly persons with presbyacusis. A) At peak of P300 waveform. Darkest areas reflect greatest positivity. B) At trough of mismatched negativity (MMN) waveform. Darkest areas reflect greatest negativity.

of verbal tasks, similar effects have been observed in patients with multiple sclerosis,[11-13] patients suffering cranial trauma,[14] and patients who have undergone commissurotomy.[15-17] This background led us to suggest that the corpus callosum must necessarily be suspected of playing a key role in the various asymmetries we have illustrated above. The rationale for this position is based on two key assumptions: 1) with only rare exceptions, verbal tasks are mediated by the left hemisphere, and nonverbal tasks by the right hemisphere[18,19]; and 2) by virtue of the anatomy of the crossed and uncrossed auditory pathways, the right ear has privileged access to the left hemisphere, while the left ear enjoys similar privileged access to the right hemisphere (eg, Zaidel[20]). We suggest, therefore, that with age there is a progressive loss in the efficiency of interhemispheric transfer of auditory information.[21] Like so many other manifestations of aging, this effect may be expected to vary widely among elderly persons. In its extreme form, it is revealed by a marked left ear deficit on standard dichotic verbal tasks.

To the extent that the demonstrated asymmetries are related to callosal dysfunction, two important clinical implications are suggested. First, aspects of binaural function other than dichotic listening may be compromised (eg, Warren et al[22] and Martin and Cranford[23]). The ability to structure auditory space into auditory foreground (attended talker) and background (competing speech or noise) may be affected by this deficit in binaural function, and may, perhaps, underlie the common complaint of elderly persons that speech is difficult to understand in the presence of background noise.

Second, the common symptom reported by the parents and teachers of children with a speech processing deficit, that the child has unusual difficulty understanding speech in noisy environments, may, as Frank Musiek and his colleagues[24] have suggested, be a manifestation of delayed or faulty development of callosal myelination.

ACKNOWLEDGMENTS — This research reflects the collective and dedicated efforts of Rose Chmiel, Emily Murphy, Craig Jordan, John Allen, Henry Lew, Amy Wilson, Mohammad Shaker, Noriko Sonobe, Susan Eicher, Joel Anthis, and Jeff Davis.

REFERENCES

1. Jerger J, Jerger S, Oliver T, Pirozzolo F. Speech understanding in the elderly. Ear Hear 1989;10:79-89.

2. Jerger J, Jerger S, Pirozzolo F. Correlational analysis of speech audiometric scores, hearing loss, age, and cognitive

abilities in the elderly. Ear Hear 1991;12:103-9.

3. Jerger J, Jordan C. Age increases asymmetry on a cued-listening task. Ear Hear 1992;13:272-7.

4. Jerger J, Darling R, Florin E. Efficacy of the cued-listening task in the evaluation of binaural hearing aids. J Am Acad Audiol 1994;5:279-85.

5. Jerger J, Stach B, Johnson K, Loiselle L, Jerger S. Patterns of abnormality in dichotic listening. In: Jensen J, ed. Presbyacusis and other age related aspects. Copenhagen, Denmark: Stougaard Jensen, 1990:143-50.

6. Jerger J, Chmiel R, Allen J, Wilson A. Effects of age and gender on dichotic sentence identification. Ear Hear 1994;15:273-85.

7. Fifer R, Jerger J, Berlin C, Tobey E, Campbell J. Development of a dichotic sentence identification test for hearing-impaired adults. Ear Hear 1983;4:300-5.

8. Jerger J, Alford B, Lew H, Rivera V, Chmiel R. Dichotic listening, event-related potentials and interhemispheric transfer in the elderly. Ear Hear 1995;16:482-98.

9. Jasper H. The ten-twenty system of the International Federation. Electroencephalogr Clin Neurophysiol 1958;15:115-7.

10. Kraus N, McGee T, Micco A, Sharma A, Carrell T, Nicol T. Mismatch negativity in school-age children to speech stimuli that are just perceptibly different. Electroencephalogr Clin Neurophysiol 1993;88:123-30.

11. Lindeboom J, Horst R. Interhemispheric disconnection effects in multiple sclerosis. J Neurol Neurosurg Psychiatry 1988;51:1445-7.

12. Rao S, Bernardin L, Leo G, Ellington L, Ryan S, Burg L. Cerebral disconnection in multiple sclerosis. Relationship to atrophy of the corpus callosum. Arch Neurol 1989;46:918-20.

13. Rubens AB, Froehling B, Slater G, Anderson D. Left ear suppression on verbal dichotic tests in patients with multiple sclerosis. Ann Neurol 1985;18:459-63.

14. Bergman M, Hirsch S, Solzi P. Interhemispheric suppression: a test of central auditory function. Ear Hear 1987;8:87-91.

15. Milner B, Taylor S, Sperry R. Lateralized suppression of dichotically presented digits after commissural section in man. Science 1968;161:184-5.

16. Sparks R, Geschwind N. Dichotic listening in man after section of the neocortical commissures. Cortex 1968;4:3-16.

17. Springer SP, Sidtis J, Wilson D, Gazzinaga MS. Left ear performance in dichotic listening following commissurotomy. Neuropsychologia 1978;16:305-12.

18. Hellige J. Hemispheric asymmetry: what's right and what's left. Cambridge, Mass: Harvard University Press, 1993.

19. Hugdahl K, ed. Handbook of dichotic listening: theory, methods and research. New York, NY: John Wiley & Sons, 1988.

20. Zaidel E. Disconnection syndrome as a model for laterality effects in the normal brain. In: Hellige J, ed. Cerebral hemisphere asymmetry. New York, NY: Praeger, 1983:95-151.

21. Goldstein G, Shelly C. Does the right hemisphere age more rapidly than the left? J Clin Neuropsychol 1981;3:67-78.

22. Warren L, Wagener J, Herman G. Binaural analysis in the aging auditory system. J Gerontol 1978;33:731-6.

23. Martin D, Cranford J. Age-related changes in binaural processing: II. Behavioral findings. Am J Otol 1991;12:365-9.

24. Musiek F, Gollegly K, Baran J. Myelination of the corpus callosum and auditory processing problems in children: theoretical and clinical correlates. Semin Hear 1984;5:231-40.

Ann Otol Rhinol Laryngol 106:1997

NEUROBEHAVIORAL STUDIES OF THE CENTRAL AUDITORY SYSTEM

R. BRUCE MASTERTON, PHD†
TALLAHASSEE, FLORIDA

The history of ablation-behavior experimentation into the central auditory system has led to conclusions not obviously derivable from knowledge of neuroanatomy or neurophysiology alone. 1) The ventral, and not the dorsal, acoustic stria is necessary and sufficient for discriminating the physical dimensions of sound. 2) The ventral, and not the dorsal, system is also necessary and sufficient for discriminations of both the azimuth and elevation of a sound source. 3) A functional "acoustic chiasm" is centered in the superior olivary complex, resulting in the neurobehavioral "representation" of each acoustic hemifield only in the contralateral side of the central system (despite the presence of ipsilateral activity). 4) The behavioral usefulness of the ipsilateral activity present above the superior olivary complex, the role of the entire dorsal acoustic system, and the role of the descending system remain unknown. The fact that the only clear structural-behavioral correspondence yet known is that between the superior olives and sound localization seems to suggest that the more fruitful avenues of further inquiry into the roles of the central auditory system might lie in the more biologic (or Darwinian) as opposed to the physical (or Helmholtzian) dimensions of auditory processing.

KEY WORDS — acoustic stria, auditory cortex, inferior colliculus, superior olivary complex.

The modern era of neurobehavioral studies of the central auditory system can be dated to the late 1940s, when Harlow Ades and Dewey Neff returned from the armed forces to set up experimental laboratories at the Universities of Rochester and Chicago, respectively. Together with their students, they began a systematic exploration of the behavioral role of the auditory cortex, mostly by the ablation-behavior method (eg, Raab and Ades,[1] Neff and Hind,[2] and Butler et al[3]). After pretraining and testing of discriminations of carefully controlled auditory stimuli, circumscribed ablations were performed and then postoperative retraining and retesting of the same discriminations were administered. When Irving Diamond joined the Neff group at Chicago, he added careful histologic verification of the lesion along with the distribution of the resulting thalamic retrograde degeneration.

Since that time, ablation-behavior testing of the roles of structures in the central auditory system has progressed a long way. Neurobehavioral studies now range over most of the auditory nuclei, from hindbrain to forebrain, and whether nuclear ablations or tract sections, lesions are now based entirely on up-to-date knowledge of the neuroanatomy and physiology of the system. Histologic verifications of lesions now often include retrograde or orthograde axonal transport methodology as well as lesion reconstruction.

Behavioral training and testing methods have also come a long way.[4] Although postoperative testing always begins with a repetition of the preoperative tests, it also includes further intensive and extensive testing to circumscribe any deficit that might be present or to illustrate the lack of ancillary deficits over a wide variety of discriminations. In addition, ablation-behavior methods now pay close attention to the role of the particular motor response and motivational requirements of the behavioral task used to indicate discrimination.[5,6] In the brief summary that follows, each of these considerations is taken into account.

DISCRIMINATIONS OF PHYSICAL DIMENSIONS OF SOUND

To begin with, we now know that an animal's audiogram and its ability to make frequency (or FM) discriminations or intensity (or AM) discriminations does *not* depend on the auditory cortex nor on any one structure along the pathway. However, these discriminations do depend entirely on the "ventral acoustic system," consisting of the ventral cochlear nucleus, ventral acoustic striae, trapezoid body, and lateral lemniscus. The evidence for this conclusion is that ablation of the *dorsal* acoustic system, consisting of dorsal cochlear nucleus or dorsal and intermediate acoustic stria, has *no* detectable effect on any of these tests. That is, absolute sensitivity across an animal's range of hearing (as in audiometry) or thresholds for frequency or intensity discriminations are entirely unaffected by dorsal system lesions.[4] In sharp con-

---

From the Departments of Psychology, Psychobiology, and Neuroscience, Florida State University, Tallahassee, Florida. Supported by the National Institutes of Health (DC00197, DC02037, and NS07726). This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Florida State University.

†Deceased December 1996.

trast, the same discriminations are permanently affected by almost any hindbrain lesion that intrudes on the ventral system, with the more complete lesions resulting in more complete deficits.

The conclusion implied, namely, that the dorsal cochlear nucleus plays no role in hearing, is absurd, of course. Nevertheless, the fact remains that not one physical dimension of sound yet tested has ever revealed a deficit after complete ablation of the dorsal acoustic system.

Even the ventral acoustic system (on which discrimination of each of the physical dimensions of sound *does* seem to depend) is itself entirely dependent on discriminations performed earlier in the system, that is, by the cochlea itself. Therefore, the central system seems to add little or nothing to the discriminative capacity of the cochlea beyond what might be expected from the involvement of a population of neurons with nonidentical tuning curves and carry the cochlea's output to an ultimate attachment to any one of a variety of motor or "output" systems. This conclusion, in turn, has redirected the neurologic analysis of the central system away from the physical dimensions of sound, toward more biologic dimensions of sound and of sound sources.

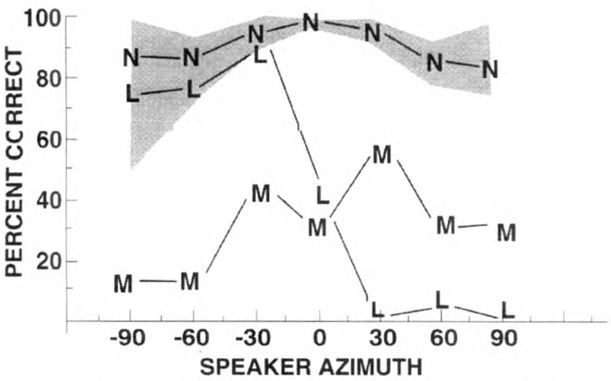
DISCRIMINATIONS OF DIMENSIONS OF SOUND SOURCES

The physiological fate of the neural activity evoked by sound and its dispersion throughout the central auditory system led to frustration among early experimentalists. The question arose: If the central auditory system is not necessary for the analysis of sound, then what is it for? The first answer to this question was suggested by the Neff laboratory. Neff's group[7-9] showed that after cortical ablation, an animal suffered a profound, though temporary, deficit in localizing the source of a sound in space. Mark Rosenzweig[10] and his colleagues (eg, Rosenzweig and Sutton[11]) soon showed that the potentials evoked by sound showed binaural interactions at the level of the lateral lemniscus and every level above. Since no binaural interaction was evident at the trapezoid body,[12] they reasoned that structures between the trapezoid body and the lateral lemniscus were responsible for binaural interaction (and, probably, azimuth encoding). At about the same time, Stotler[13] and Rasmussen[14] explored the anatomic basis of azimuth analysis by showing the convergence of the second-order fibers in the trapezoid body onto the superior olives. Single unit studies, first by Galambos et al,[15] showed the presence of interaural time sensitive cells in the *medial* superior olive (MSO; for a modern analysis of the role of MSO, see Yin and Chan[16,17]), while Boudreau and Tsuchitani[18] showed that the *lateral* superior olive (LSO) was an exquisite analyzer of interaural spectrum differences. Between the MSO and LSO, both binaural cues for sound-source azimuth (Δt and ΔI) seemed adequately analyzed for azimuth, and neurobehavioral experiments verified this necessity both with surgical and "natural" ablations (eg, see Masterton et al[19-21]).

One of the corollary results of the evoked potential studies of Rosenzweig[10] was that a sound in space evoked activity on both sides of the central system. This fact has been repeatedly verified many times from hindbrain to forebrain either with auditory brain stem responses, with single unit studies, or with 2-deoxyglucose scanning, and this fact is now often used in clinical diagnosis. The presence of activity on both sides of the system, even with stimuli confined to one ear alone, also suggested that the physiological substrate of a sound localizable to one side of the head or the other was probably the result of the *imbalance* of neural activity on the two sides of the central system. Although evoked activity, regardless of how it is measured, is always greater contralateral to the sound source, activity ipsilateral to the sound source is invariably present. Rosenzweig interpreted this result in the most reasonable way then available, namely, that it was the *ratio* of the activity between the two sides of the system that was the probable physiological substrate for the azimuth of a sound source. This idea of the ratio of activity between the two sides of the central system became the predominant explanation of sound localization and its deficits for years to come (eg, see Starr[22]).

Because of the adequacy of this "ratio theory" of azimuth perception, it was the 1970s before it was realized that if the azimuth of a sound source was indeed encoded as the *ratio* of activity between the two sides of the system, then a unilateral lesion should collapse the entire azimuth dimension. That is, if a unilateral ablation entirely abolished activity on one side of the central pathway, sound localization in the horizontal plane should be entirely abolished also (by reducing to zero either the numerator or the denominator of the ratio). Yet Neff's group had shown that a unilateral lesion of auditory cortex seemed to have only a transient effect on azimuth discrimination.[9]

It was some years later before Thompson and Masterton[23] and Jenkins and Masterton[24] were led to retest the ratio theory of sound localization. They showed that a unilateral lesion anywhere *above* the superior olives (that is, section of the lateral lemniscus or brachium of the inferior colliculus or ablation of the inferior colliculus, medial geniculate, or auditory cortex) produced a profound deficit only contralateral to the lesion, while sound localization abil-



Behavioral performance of cats in 7-choice, water-reward, sound localization tests. Mean (N) and entire range (gray area) for 9 normal cats; M — monaural cat with right cochlea destroyed; L — cat with left lateral lemniscus sectioned. Note "chiasm"-like difference between lemniscus (L) and monaural (M) cases (see Jenkins and Masterton[24]). Although these results were obtained with reward test, similar results are obtained for same lesions and stimuli with shock-avoidance tests.

ity in the acoustic hemifield ipsilateral to the lesion remained essentially normal. If the lesion was *below* the level of the superior olive (say, in one cochlea or in the trapezoid body), then deficits were seen in both hemifields of space (see Figure[24]). In addition to showing the contrasting deficits resulting from unilateral lesions above and below the superior olives, they also showed how these deficits were missed in the earlier behavioral experiments.[24] This same result has now been shown in opossums,[25] rats,[26] ferrets,[27] and monkeys.[28]

Curiously, the outcome of the behavioral experiments of Thompson and Masterton[23] and of Jenkins and Masterton[24] and Jenkins and Merzenich[29] seemed to duplicate the contrasting results of lesions of the *visual* system above and below the *optic* chiasm. Glendenning and Masterton[30] noticed that the strictly contralateral deficit resulting from a unilateral lesion *above* the superior olivary complex (SOC), as opposed to bilateral or ipsilateral deficits resulting from lesions *below* the SOC, was functionally similar to that seen in vision after lesions in the optic tract, as opposed to the optic nerve. Glendenning et al[31-34] termed this behavioral effect the "acoustic chiasm" and set out to discover its anatomic substrate.

As it turns out, the acoustic "chiasm," though *functionally* identical to the optic and somatosensory chiasms, is far from anatomically identical. That is, whereas the optic and somatosensory "chiasms" are commissures merely requiring the proper sorting of ascending fibers, the acoustic chiasm is a physiological process as well. Although this chiasmatic process is centered in the SOC, it depends on a precise convergence of inhibitory and excitatory activity, both among its afferents and efferents.[33] And it, too, depends entirely on the ventral acoustic system, and not at all on the dorsal system.

Given this dependence of azimuth discrimination on the hindbrain's ventral acoustic system, Sutherland[35,36] tested the possibility that the *dorsal* system might be the substrate for the discrimination of sound source elevation, using both the reflex method of Thompson and Masterton[23] and the rigorous training and testing methods of Jenkins and Masterton.[24] At first it appeared that the dorsal system was indeed necessary for discriminations of elevation — a cat deprived of its dorsal system can *not* orient accurately to an elevated source of unexpected noise burst.[35] However, the same lesion turned out to be entirely ineffective in producing a deficit in passive discriminations of elevated sound sources.[37] Once more, lesions of the ventral system alone abolished the elevation discrimination in the same manner as they did for azimuth discrimination.[38]

In summary, the history of ablation-behavior experimentation into the central auditory system has led to conclusions not obviously derivable from knowledge of neuroanatomy or neurophysiology alone: 1) the ventral, and not the dorsal, acoustic stria is necessary and sufficient for discriminating the physical dimensions of sound; 2) the ventral, and not the dorsal, system is also necessary and sufficient for discriminations of both the azimuth and elevation of a sound source; 3) a functional "acoustic chiasm" is centered in the SOC, resulting in the neurobehavioral "representation" of each acoustic hemifield only in the contralateral side of the central system (despite the presence of ipsilateral activity); and 4) the behavioral usefulness of the ipsilateral activity present above the SOC, the role of the entire dorsal acoustic system, and the role of the descending system remain unknown at present (but see Jane et al[39]).

Finally, the fact that the only clear structural-behavioral correspondence yet known is that between the superior olives and sound localization seems to suggest that the more fruitful avenues of further inquiry into the roles of the central auditory system might lie in the more biologic (or Darwinian) as opposed to the physical (or Helmholtzian) dimensions of auditory processing (eg, Masterton[40,41]).

REFERENCES

1. Raab DH, Ades HW. Cortical and midbrain mediation of a conditioned discrimination of acoustic intensities. Am J Psychol 1946;59:59-83.

2. Neff WD, Hind JE. Auditory thresholds of the cat. J Acoust Soc Am 1955;27:480-3.

3. Butler RA, Diamond IT, Neff WD. Role of auditory cortex in discrimination of changes in frequency. J Neurophysiol 1957;20:108-20.

4. Masterton RB, Granger ME. Role of the acoustic striae in hearing: contribution of dorsal and intermediate striae to detection of noises and tones. J Neurophysiol 1988;60:1841-60.

5. Heffner HE, Masterton RB. Contribution of auditory cortex to sound localization in the monkey (*Macaca mulatta*). J Neurophysiol 1975;38:1340-58.

6. LeDoux JE, Sakaguchi A, Reis DJ. Subcortical efferent projections of the medial geniculate nucleus mediate emotional responses conditioned to acoustic stimuli. J Neurosci 1984;4:683-98.

7. Neff WD, Arnott GP, Fisher JF. Function of auditory cortex: localization of sound in space [Abstract]. Am J Physiol 1950;163:738.

8. Neff WD, Fisher JF, Diamond IT, Yela M. Role of auditory cortex in discrimination requiring localization of sound in space. J Neurophysiol 1956;19:500-12.

9. Neff WD. Localization and lateralization of sound in space. In: DeReuch AVS, Knight J, eds. Ciba Foundation Symposium. Hearing mechanisms in vertebrates. London, England: J and A Churchill Ltd, 1968:207-31.

10. Rosenzweig MR. Cortical correlates of auditory localization and of related perceptual phenomena. J Comp Physiol Psychol 1954;47:269-76.

11. Rosenzweig MR, Sutton D. Binaural interaction in lateral lemniscus of cat. J Neurophysiol 1958;21:17-23.

12. Rosenzweig MR, Amon AH. Binaural interaction in the medulla of the cat. Experientia 1955;11:498-500.

13. Stotler WA. An experimental study of the cells and connections of the superior olivary complex of the cat. J Comp Neurol 1953;98:401-32.

14. Rasmussen GL. Efferent connections of the cochlear nucleus. In: Graham AB, ed. Sensorineural hearing processes and disorders. Boston, Mass: Little, Brown, 1967:61-75.

15. Galambos R, Schwartzkopff J, Rupert A. Microelectrode studies of superior olivary nuclei. Am J Physiol 1959;197:527-36.

16. Yin TCT, Chan JCK. Neural mechanisms underlying interaural time sensitivity to tones and noise. In: Edelman GM, Gall WE, Cowan WM, eds. Auditory function. New York, NY: Wiley, 1988:385-430.

17. Yin TCT, Chan JCK. Interaural time sensitivity in the medial superior olive of the cat. J Neurophysiol 1990;64:465-88.

18. Boudreau JC, Tsuchitani C. Cat superior olive S-segment cell discharge to tonal stimulation. In: Neff WD, ed. Contributions to sensory physiology. Vol 4. New York, NY: Academic Press, 1970:143-213.

19. Masterton RB, Jane JA, Diamond IT. The role of brainstem auditory structures in sound localization. I: Trapezoid body, superior olive and lateral lemniscus. J Neurophysiol 1967;30:341-59.

20. Masterton RB, Jane JA, Diamond IT. The role of brainstem auditory structures in sound localization. II: Inferior colliculus and its brachium. J Neurophysiol 1968;31:96-108.

21. Masterton RB, Thompson GC, Bechtold JK, Robards MJ. Neuroanatomical basis of binaural phase-difference analysis for sound localization: a comparative study. J Comp Physiol Psychol 1975;89:379-86.

22. Starr A. Neurophysiological mechanisms of sound localization. Fed Proc 1974;33:1911-4.

23. Thompson GC, Masterton RB. Brainstem auditory pathways involved in reflexive head orientation to sound. J Neurophysiol 1978;41:1183-202.

24. Jenkins WM, Masterton RB. Sound localization: effects of unilateral lesions in central auditory system. J Neurophysiol 1982;47:987-1016.

25. Jenkins WM. Contribution of the inferior colliculus to sound localization in the Virginia opossum (*Didelphis virginiana*) [Thesis]. Tallahassee, Fla: Florida State University, 1976.

26. Kelly JB, Judge PW. Effects of medial geniculate lesions of sound localization by the rat. J Neurophysiol 1985;53:361-72.

27. Kelly JB, Kavanagh GL. Sound localization after unilateral lesions of inferior colliculus in the ferret (*Mustela putorius*). J Neurophysiol 1994;71:1078-86.

28. Heffner HE, Heffner RS. Lateralization of the perception of communicative vocalizations in Japanese macaques. In: Anderson JR, Roeder JJ, Thierry B, Heffenschmidt N, eds. Current primatology. Strasbourg, France: Universite Louis Pasteur, 1994:1-8.

29. Jenkins WM, Merzenich MM. Role of cat primary auditory cortex for sound-localization behavior. J Neurophysiol 1984;52:819-47.

30. Glendenning KK, Masterton RB. Acoustic chiasm: efferent projections of lateral superior olive. J Neurosci 1983;3:1521-37.

31. Glendenning KK, Hutson KA, Nudo RJ, Masterton RB. Acoustic chiasm II: anatomical basis of binaurality in lateral superior olive of cat. J Comp Neurol 1985;232:261-85.

32. Glendenning KK, Masterton RB, Baker BN, Wenthold RJ. Acoustic chiasm III: nature, distribution and sources of afferents to the lateral superior olive in the cat. J Comp Neurol 1991;310:377-400.

33. Glendenning KK, Baker BN, Hutson KA, Masterton RB. Acoustic chiasm V: inhibition and excitation in the ipsilateral and contralateral projections of LSO. J Comp Neurol 1992;319:100-22.

34. Hutson KA, Glendenning KK, Masterton RB. Acoustic chiasm IV: eight midbrain decussations of the auditory system in the cat. J Comp Neurol 1991;312:105-31.

35. Sutherland DP. Study of the role of the dorsal acoustic stria in orientation to elevated sound sources [Thesis]. Tallahassee, Fla: Florida State University, 1991.

36. Sutherland DP. Elevation discrimination in cats: Role of central auditory structures [Dissertation]. Tallahassee, Fla: Florida State University, 1994.

37. Masterton RB, Sutherland DP. Discrimination of sound source elevation in cats: I. role of dorsal/intermediate and ventral acoustic striae [Abstract]. Assoc Res Otolaryngol Abstr 1994:84.

38. Sutherland DP, Masterton RB. Discrimination of sound source elevation in cats: II. role of inferior colliculus, medial geniculate, and auditory cortex [Abstract]. Assoc Res Otolaryngol Abstr 1994:84.

39. Jane JA, Masterton RB, Diamond IT. The function of the tectum for attention to auditory stimuli in the cat. J Comp Neurol 1965;125:165-92.

40. Masterton RB. Role of the central auditory system in hearing: the new direction. Trends Neurosci 1992;15:280-5.

41. Masterton RB. Central auditory system. ORL J Otorhinolaryngol Relat Spec 1993;55:159-63.

Ann Otol Rhinol Laryngol 106:1997

SPEECH INTELLIGIBILITY OF CHILDREN WITH MULTICHANNEL COCHLEAR IMPLANTS

RICHARD T. MIYAMOTO, MD
MARIO SVIRSKY, PHD
KAREN ILER KIRK, PHD
AMY M. ROBBINS, MS
SUSAN TODD, MS
ALLISON RILEY, MS
INDIANAPOLIS, INDIANA

The purpose of this longitudinal study is to document improvements in speech intelligibility in children who have received multichannel cochlear implants, to compare their performance to that of a matched group of children with different levels of hearing loss who use conventional hearing aids. Speech intelligibility was measured by panels of listeners who analyzed recorded speech samples preimplant and at 6-month intervals following implantation. The results of this study demonstrate that prelingually deafened children with the Nucleus multichannel cochlear implant achieved significant improvements in speech intelligibility. By the 4.5- to 7.5-year intervals, the speech intelligibility exceeded 40%.

KEY WORDS — multichannel cochlear implant, speech intelligibility.

INTRODUCTION

The development of intelligible speech is an elusive goal for many prelingually deaf children who receive minimal benefit from conventional amplification. With the advent of multichannel cochlear implantation, the segmental features of speech requiring high-frequency information are now accessible. However, speech perception skills emerge over a long time course[1-5] and are a prerequisite to effective speech production. The purpose of this comprehensive, longitudinal study is to 1) document improvements in speech intelligibility over time and 2) to compare the cochlear implant (CI) children's performance to the performance of a matched group of children with different levels of hearing impairment who use hearing aids.

MATERIAL AND METHODS

Subjects. Speech intelligibility was measured in children with prelingual deafness who had received the Nucleus multichannel CI. Their mean age at onset of deafness was 0.8 years, and the mean age at implantation was 5.0 years.

The speech intelligibility of the implanted subjects was compared to that of subjects who used conventional hearing aids. The hearing aid users were divided into three categories based on their unaided thresholds at 500, 1,000, and 2,000 Hz. "Gold" hearing aid users demonstrated levels of 90 to 100 dB hearing level (HL) at two of three frequencies. "Silver" hearing aid users demonstrated hearing levels of 101 to 110 dB HL. "Bronze" hearing aid users demonstrated thresholds over 110 dB HL. All of the children who received a CI were in the bronze hearing aid range preoperatively.

Procedures. Each subject produced 10 sentences that were repeated after an examiner's spoken model. For children under 6 years, one list of the Beginner's Intelligibility Test (BIT) was administered. The BIT utilizes objects and pictures to convey the target sentence, and an imitative response is elicited. Older children (>6 years) who could read were given the Monsen Sentences Test. For this procedure, children read the sentences and then imitated the examiner's spoken model. Each subjects' sentence productions were audio recorded, digitized, randomized, and then played to panels of listeners who transcribed what they thought the subject had said. Panels consisted of three listeners with no prior experience in listening to the speech of persons with hearing loss. Each set of 10 sentences produced by 1 subject was evaluated by a single panel. The listeners evaluated more than one set of sentences, but each set was produced by a new subject, and contained a sentence list not previously heard by the panel. Individual subject intelligibility scores were calculated by averaging the number of words correctly understood across the three listeners.[6,7]

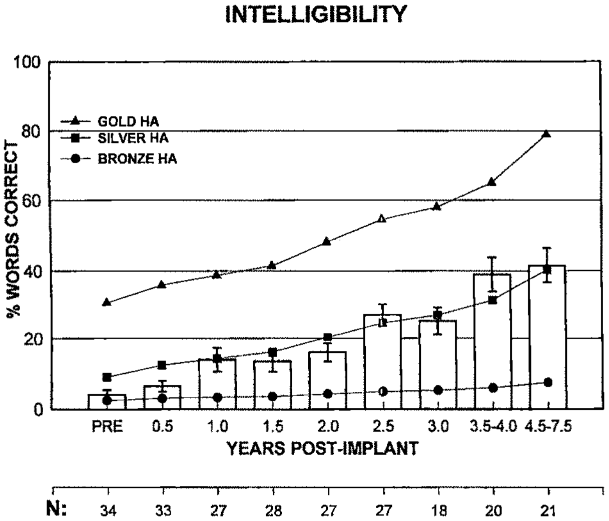
RESULTS

Illustrated on the Figure are the mean speech intelligibility scores for the groups of subjects calculated at 6-month intervals. The three superimposed curves indicate the expected average intelligibility for three groups of hearing aid users (gold, silver, and

---

From the Department of Otolaryngology–Head and Neck Surgery, Indiana University School of Medicine, Indianapolis, Indiana. Supported by National Institutes of Health/National Institute on Deafness and Other Communication Disorders.

CORRESPONDENCE — Richard T. Miyamoto, MD, Dept of Otolaryngology–Head and Neck Surgery, Indiana University School of Medicine, 702 Barnhill Dr, Suite 0860, Indianapolis, IN 46202.



Average speech intelligibility achieved by prelingually deafened, pediatric cochlear implant users. Number (N) of subjects evaluated at each interval is indicated at bottom. Error bars show standard error of mean at each interval. Three superimposed curves indicate expected average intelligibility for three groups of hearing aid (HA) users (gold, silver, and bronze), at same ages as cochlear implant subjects in corresponding bar.

bronze), at the same ages as the CI subjects in the corresponding bar. The expected values for the hearing aid users were calculated from linear regressions that were generated from measurements taken from 67 gold, 50 silver, and 35 bronze hearing aid users.

The graph shows that CI children start at intelligibility levels that are similar to levels expected from bronze hearing aid users. This is not unexpected, considering that most of the CI children were, in fact, bronze hearing aid users prior to implantation. The CI children improve their intelligibility faster than silver hearing aid users, so after 1 to 2.5 years postimplant they have reached the average intelligibility levels associated with silver hearing aid users of the same age. Continued improvement is seen throughout the postimplant period. The implanted children have not yet reached a plateau.

DISCUSSION

The results of this study demonstrate that prelingually deafened children with the Nucleus multichannel CI achieve significant improvements in speech intelligibility. Although speech intelligibility improves at a slower rate than speech perception abilities, the longitudinal trends are encouraging. The average speech intelligibility of the CI subjects prior to implantation was close to 0%. After 1 to 2.5 years of implant use, the children reached the intelligibility levels achieved by the silver hearing aid users of the same age. By the 4.5- to 7.5-year interval, the speech intelligibility exceeded 40%.

With the current trend toward earlier implantation, auditory experience with CIs will more closely approximate the experience gained by the hearing aid users. The benefits of earlier implantation will be the focus of future communication research.

REFERENCES

1. Miyamoto RT, Osberger MJ, Robbins AM, Myres WA, Kessler KK, Pope ML. Longitudinal evaluation of communication skills of children with single- or multi-channel cochlear implants. Am J Otol 1992;13:215-22.

2. Miyamoto RT, Osberger MJ, Robbins AM, Myres WA, Kessler KK, Pope ML. Comparison of speech perception abilities in deaf children with hearing aids or cochlear implants. Otolaryngol Head Neck Surg 1991;104:42-6.

3. Fryauf-Bertschy R, Tyler RS, Kelsay DM, Gantz BJ. Performance over time of congenitally and postlingually deafened children using a multichannel cochlear implant. J Speech Hear Res 1992;35:913-20.

4. Staller SJ, Dowell RC, Beiter AL, Brimacombe JA. Perceptual abilities of children with the Nucleus 22-channel cochlear implant. Ear Hear 1991;12(suppl 4):345-475.

5. Waltzman SB, Cohen NL, Spivak L, et al. Improvement in speech perception and production abilities in children using a multichannel cochlear implant. Laryngoscope 1990;100:240-3.

6. Osberger MJ, Robbins AM, Todd SL, Riley AI, Magmata RT. Speech production skills of children with multichannel cochlear implants. In: Hochmair-Desoyer IJ, Hochmair ES, eds. Advances in cochlear implants. Vienna, Austria: Manz, 1994:503-8.

7. Miyamoto RT, Kirk KI, Robbins AM, Todd S, Riley K. Speech perception and speech production skills of children with multichannel cochlear implants. Acta Otolaryngol (Stockh) 1996; 116:240-3.

Ann Otol Rhinol Laryngol 106:1997

EFFECTS OF EARLY DEAFNESS ON DEVELOPMENT OF BRAIN STEM AUDITORY NEURONS

THOMAS N. PARKS, PHD

SALT LAKE CITY, UTAH

Early destruction of the otocyst (embryonic precursor of the inner ear) in chick embryos results in complex changes in developing central auditory pathways. In the cochlear nucleus angularis (NA) and nucleus magnocellularis (NM), 30% to 40% of the neurons die after otocyst removal, the survivors are shrunken, and some neurons in the NA migrate to an abnormal position in the brain stem. The characteristic forms of cochlear nucleus neurons develop normally in the absence of cochlear nerve input, however. In the nucleus laminaris (NL), development of normal dendritic size is dependent on a normal inner ear, but most of the highly specialized dendritic organization of this nucleus, which is important for low-frequency sound localization, can develop normally in the absence of cochlear influences. Otocyst removal induces formation of a permanent functional aberrant axonal projection to the ipsilateral NM from the contralateral NM. Although these aberrant axons form functional glutamatergic synapses, these synapses show immature functional properties, suggesting that cochlear nerve inputs are necessary for normal maturation of glutamate receptors on auditory neurons. Treatment of chick embryos for a brief period in ovo with 6-cyano-7-nitroquinoxaline-2,3-dione, a quinoxalinedione antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate–kainate subtype of glutamate receptor, completely and permanently prevents the neuronal loss in the NM produced by otocyst removal. The work reviewed has 1) identified aspects of development in central auditory neurons that are perturbed by profound early sensorineural loss, 2) identified aspects of development that appear independent of cochlear influences, and 3) suggested a potential chemotherapeutic approach to prevention of central neuronal death after early damage to the cochlea.

KEY WORDS — congenital hearing loss, glutamate receptors, neurons.

UNDERSTANDING CENTRAL CONSEQUENCES OF EARLY DEAFNESS

Hearing loss of early onset is one of the most common severe developmental disabilities, and one with far-reaching consequences for the affected child, his or her family, and society.[1] Hope that newly developed treatments can restore hearing to persons with early-onset deafness must be tempered by the knowledge that the brain does not always remain normal after early sensory deprivation or receptor damage.[2] Because of many similarities between the auditory systems of birds and mammals and the many

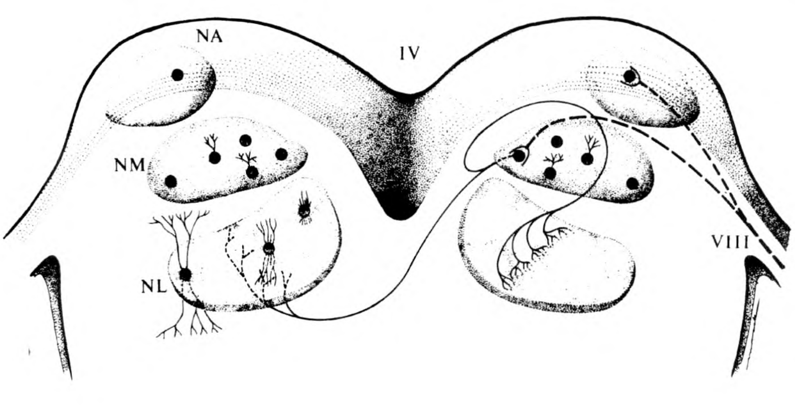


Fig 1. Schematic representation of chick brain stem auditory anatomy. Cochlear division of eighth nerve (VIII) provides tonotopic innervation of nucleus angularis (NA) and nucleus magnocellularis (NM), forming large calyx-like axonal endings in NM. Each NM neuron sends one axon branch to dorsal dendrites of neurons in ipsilateral nucleus laminaris (NL), and another branch to ventral dendrites of contralateral NL. Axon terminal fields of NM neurons are oriented perpendicularly to axis of tonotopic organization, which extends from posterolateral (representing low-frequency sounds) to anteromedial (high frequencies). This axis also defines gradient in NL dendritic length and number; cells have shorter but more numerous primary dendrites anteromedially than caudolaterally. IV — fourth ventricle.

From the Department of Neurobiology & Anatomy, University of Utah School of Medicine, Salt Lake City, Utah. This work has been supported since 1979 by the US Public Health Service, currently via a Claude E. Pepper Award from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders (5 RO1 DC00144). This research was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Utah.

CORRESPONDENCE — Thomas N. Parks, PhD, Dept of Neurobiology & Anatomy, University of Utah School of Medicine, Salt Lake City, UT 84132.

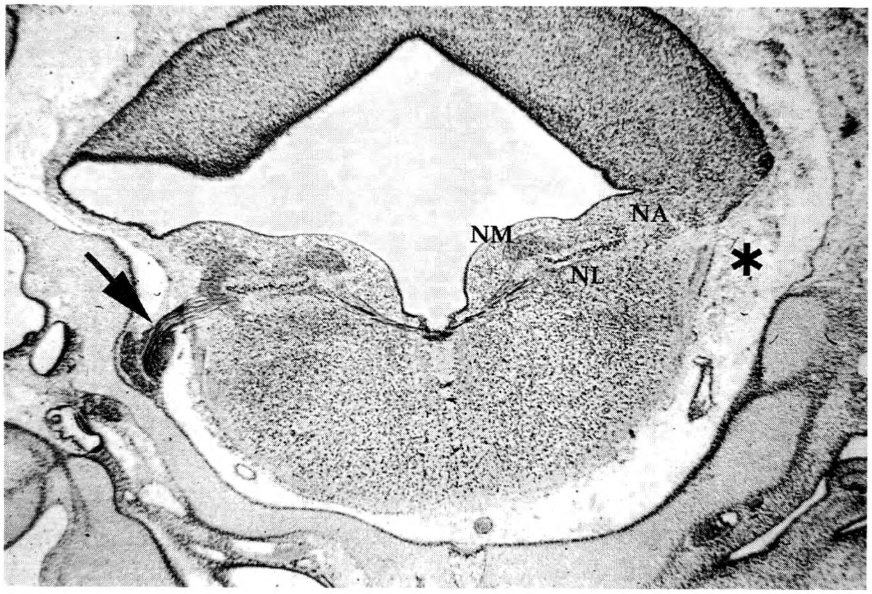


Fig 2. Photomicrograph of protargol-stained coronal section through skull and brain stem of E9 chick embryo from which right otocyst had been removed surgically on E3. Eighth nerve appears normal on unoperated left side (arrow), but is absent on right (*). Brain stem auditory nuclei (NA, NL, and NM) are present bilaterally.

advantages of using avian embryos in developmental studies,[3] we have used a chick embryo model to study the effects of early sensorineural hearing loss on development of central auditory pathways (Fig 1). This work has revealed features of the auditory system that are profoundly changed — and some that are unaffected — by early hearing loss, and has identified a potential chemotherapeutic approach to preventing the neuronal loss that follows early cochlear damage.

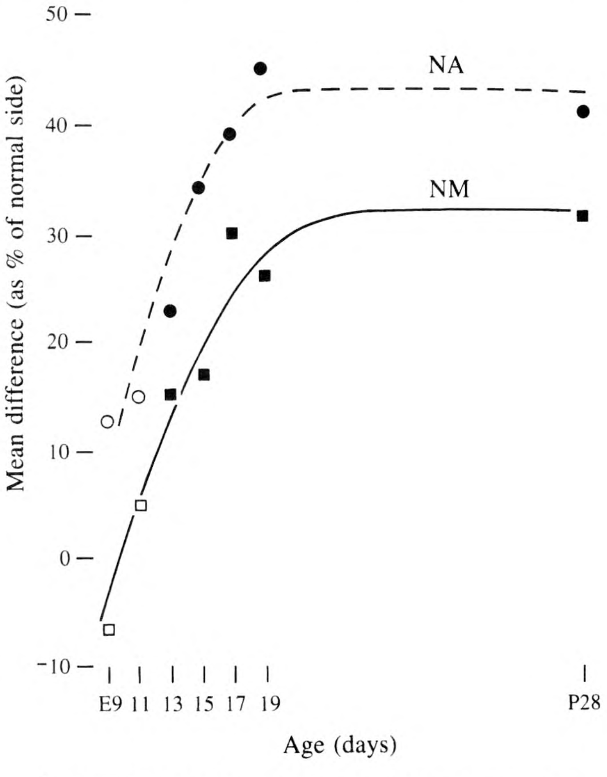


Fig 3. Effect of unilateral removal of otocyst on number of neurons in NA and NM between E9 and P28. Each symbol represents mean of percentage differences obtained by comparing neuronal number on deafferented and normal sides of brain in 3 animals at that age. Statistically significant decreases in neuronal number in both nuclei (filled symbols) are evident only after E11, when cochlear nerve normally forms functional synapses there.

DEAFENING CHICK EMBRYOS

We have used two experimental models of early hearing loss: otocyst removal and earplugs. The otocyst is the embryonic precursor of the inner ear and acousticovestibular nerve; since cochlear nerve axons do not enter the brain until E4 and the cochlea is not functional until about E11,[3] surgical removal of the otocyst on E3 results in the brain stem auditory system's developing without ever receiving synaptic input from the ear[4] (Fig 2). The otocyst can be removed unilaterally or bilaterally. Earplugs formed by injecting liquid plastic hearing aid sealer into the external auditory meatus of E18 chick embryos were initially employed to produce a fully reversible 40-dB conductive hearing loss for behavioral studies.[5] It was subsequently determined, however, that the earplugging procedure also produces some sensorineural loss and that central degenerative changes associated with ear-plugging can be attributed entirely to this sensorineural component.[6]

CHANGES IN NEURONAL NUMBER, SIZE, AND POSITION AFTER OTOCYST REMOVAL

Unilateral otocyst removal at E3 produces no detectable effects on development of the nucleus angularis (NA, comparable to mammalian posteroventral and dorsal cochlear nuclei), nucleus magnocellularis

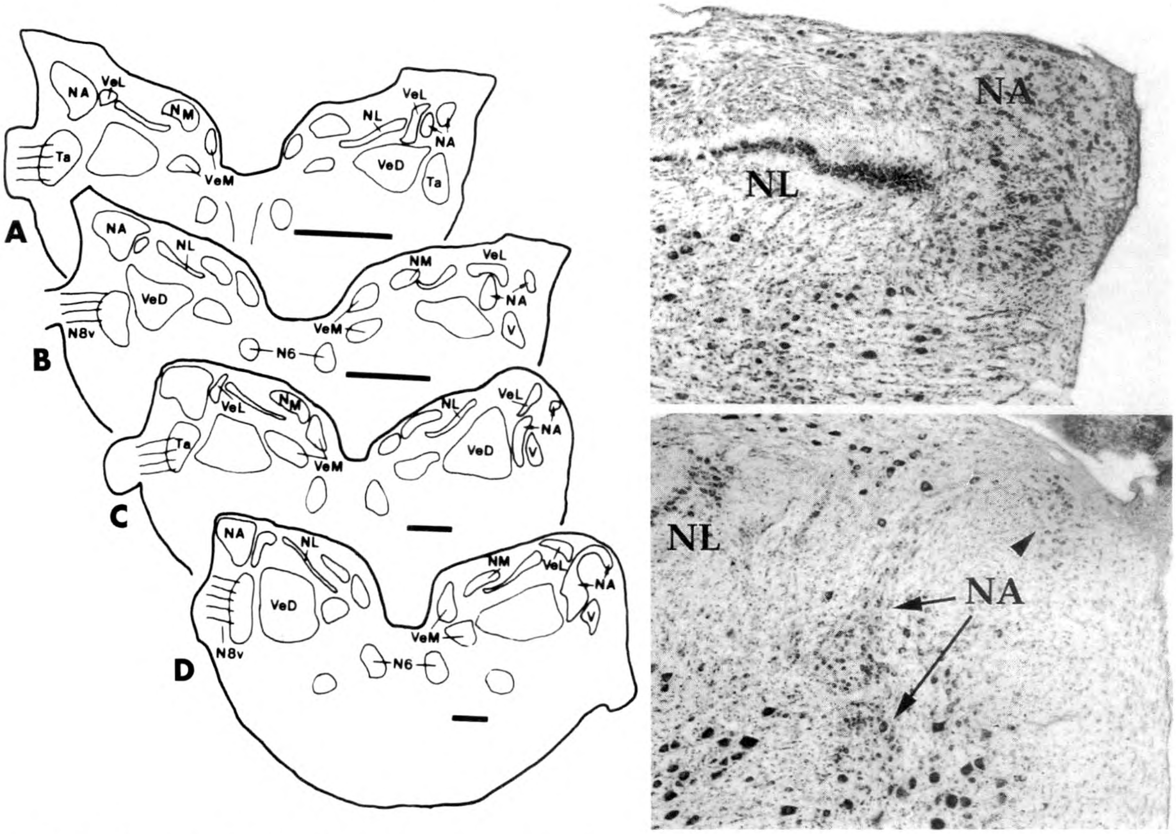


Fig 4. Tracings and photomicrographs of thionin-stained coronal sections illustrating movement of NA neurons to ectopic location following otocyst removal. In tracings, A is from E9, B from E13, C from E19, and D from P28 animal, and arrows indicate location of NA. Note movement of NA neurons on right (operated) side to abnormal ventromedial position between E9 and P28. Top photomicrograph is from normal (unoperated) side of P28 animal shown in tracing D. In lower photomicrograph, from operated side of P28 animal, small group of NA cells in normal dorsolateral position (arrowhead) is connected with larger ventromedial group of ectopic neurons (arrows) by thin column of cells. Scale bars — 0.5 mm for tracings and 0.25 mm for photomicrographs; N8v — vestibular nerve; N6 — abducens nucleus; Ta — tangential vestibular nucleus; V — vestibular nucleus neurons, undetermined subdivision; VeD — descending vestibular nucleus; VeL — lateral vestibular nucleus; VeM — medial vestibular nucleus.

(NM, comparable to mammalian anteroventral cochlear nucleus), or nucleus laminaris (NL, comparable to mammalian medial superior olivary nucleus) until about E11, at which time the cochlea and cochlear nerve synapses are becoming functional.[3] At this time, neurons in the NM and NA (but not the NL) that would normally survive begin to die, leading to deficits in neuron number of approximately 30% in the NM and 40% in the NA by E17[4] (Fig 3). There is little or no normal neuronal death in the NM, and only a little normal death in the NA. Neurons in the NA and NM also fail to increase in size normally after otocyst removal, with the result that the affected neurons are about 20% smaller than normal.[4] Of interest, in the absence of cochlear nerve input during development, a portion of the NA migrates between E9 and E19 to an ectopic ventromedial position (Fig 4).

CHARACTERISTIC NEURONAL SHAPE IN NUCLEUS MAGNOCELLULARIS DEVELOPS INDEPENDENTLY OF COCHLEAR INPUT

Nucleus magnocellularis neurons normally change from multipolar to unipolar form between E11 and E15 along a rostromedial-to-caudolateral gradient, at the same time that cochlear nerve afferents to the NM undergo a dramatic decrease in branching[7]; each NM neuron normally loses (on average) 10 dendrites. Surprisingly, otocyst removal, despite leading to death of 30% of NM neurons and shrinkage of the survivors, has no effect on the extent, timing, or spatial gradient of dendritic loss in the NM[8] (Fig 5). Unilateral ear-plugging at E18 does not affect the proportion of NM neurons that develop a late-appearing primary dendrite (40%), but it retards the growth of these dendrites by about 35% at posthatching days (P)10 and P60[9] (Fig 6). Similarly, earplugs retard posthatching growth in size of NM neurons, leading to 12% smaller neurons at P25 and P60[10] (Fig 6).

EFFECTS OF OTOCYST REMOVAL ON DENDRITIC STRUCTURE IN NUCLEUS LAMINARIS

The third-order auditory neurons of the NL have

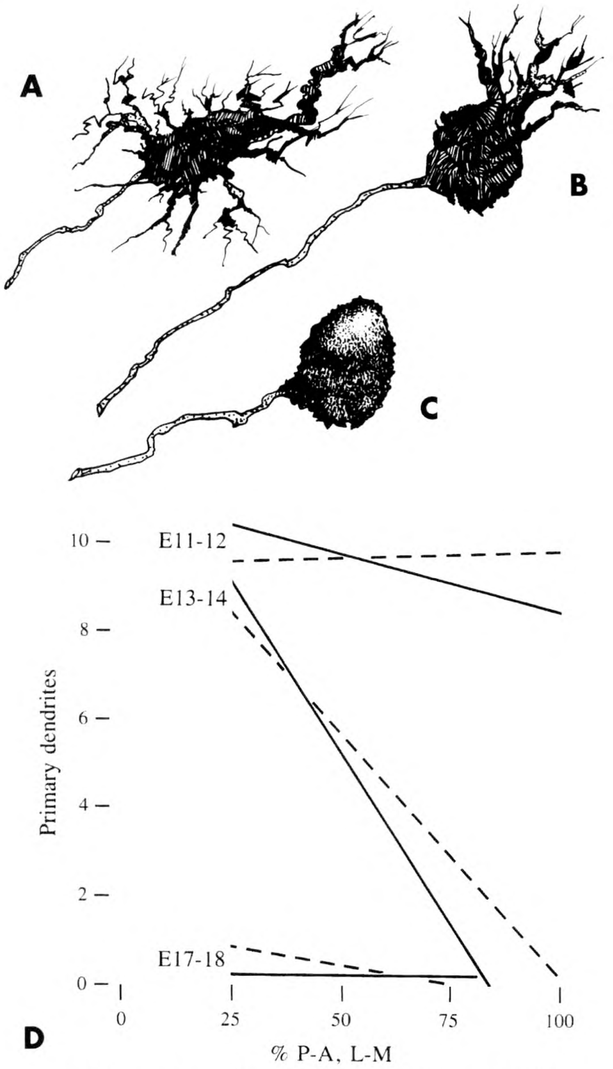


Fig 5. Illustrations of spatiotemporal gradient of dendritic loss during development of NM and independence of this process from cochlear influences. A-C) Stylized drawings of horseradish peroxidase–stained NM neurons showing normal morphologic transformation from multipolar to unipolar neurons. D) P-A — posterior to anterior, L-M — lateral to medial. At E11-12 (A), neurons throughout NM have numerous (about 10 on average) dendrites; these are rapidly lost between E13 and E16 along anteromedial-to-posterolateral gradient within NM. At E14, neurons about midway along this axis have only few dendrites (B), while more anterior cells (C) have lost all of their dendrites. By E16-17, all neurons in NM resemble neuron in C. D) Graph consists of 6 multiple linear regression lines relating number of primary dendrites to position of neurons within NM at E11-12, E13-14, and E17-18. Data are from deafferented right side of brain (dashed lines) and normally innervated left side (solid lines). There were no significant differences between deafferented and normal sides.

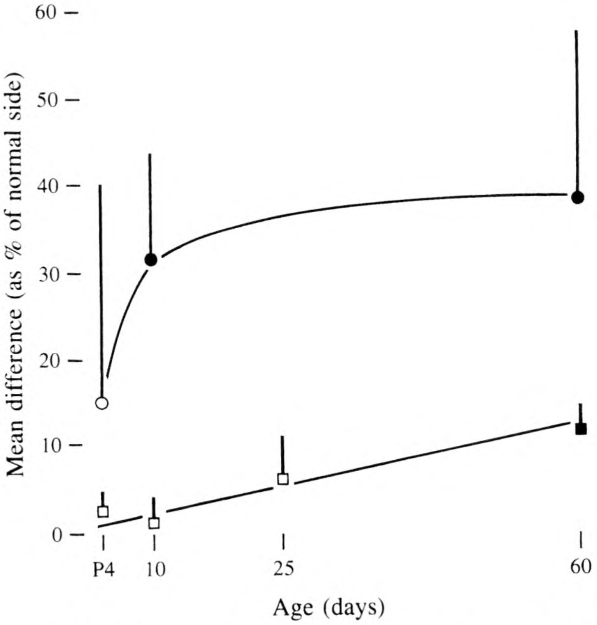


Fig 6. Effects of severe unilateral mixed conductive and sensorineural hearing loss initiated at E18 on development of neuronal cross-sectional area (squares) and total dendritic length per cell (circles) in NM. Each symbol represents mean and standard error of deprived versus normal percentage differences calculated for each of 4 to 9 animals. Hearing loss retards growth of NM neurons, producing statistically significant differences (filled symbols) in dendritic length by P10 and in cell body size by P60.

distinct dorsal and ventral dendritic tufts that receive their main synaptic input from, respectively, the ipsilateral and contralateral NM (Fig 1). Beginning about E14, and continuing for some weeks after hatching, NL neurons undergo a complex series of morphologic transformations that result in the formation of a steep anteromedial-to-posterolateral gradient of increasing total dendritic length across the nucleus.[11] Since this gradient parallels the tonotopic axis of the NL, it was hypothesized that acoustic experience might have some role in shaping the dendritic gradient. This hypothesis was tested in experiments in which one or both otocysts were removed at E3 and dendritic structure was quantified in Golgi-stained neurons from E17 embryos (Fig 7). Parks[12] found that unilateral otocyst removal resulted in a mean 44% decrease in the length of NL dendrites connected to the deafferented NM, but did not significantly affect the spatial gradient of dendritic length. Parks et al[13] found that bilateral otocyst removal had a much less severe effect than unilateral deafening on dendritic length; even this bilateral deafening, however, permitted development of relatively normal patterns of dendritic organization, including the anteromedial-to-posterolateral gradient of increasing dendritic length (Fig 1). We concluded that although attainment of normal dendritic size in the NL is dependent upon a normal inner ear, most of the highly specialized dendritic organization of this nucleus (which is undoubtedly related to the NL's key role in low-frequency sound localization) can develop normally in the complete absence of peripheral influences. These results suggested that each

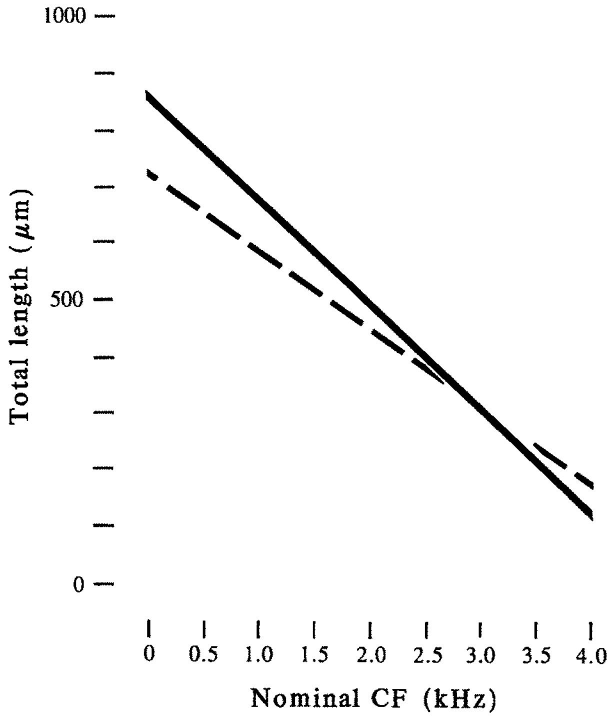


Fig 7. Regression lines showing relationship between position in NL (represented by nominal characteristic frequency [CF], which is highest at anteromedial pole of NL and lower caudolaterally) and total dendritic length for normal (solid line) and bilateral otocyst (broken line) animals. Total dendritic length is highest caudolaterally (low CF) in both groups, and slopes of normal and bilateral otocyst regression lines are not significantly different, demonstrating that spatial gradients of dendritic structure in NL can develop independently of cochlear input.

brain stem auditory nucleus is organized along an intrinsically determined axis that specifies how incoming auditory afferent axons will be organized into tonotopic arrays.

INDUCTION OF ABERRANT AUDITORY PATHWAY AFTER OTOCYST REMOVAL

To our surprise, we found that otocyst removal induces formation of an aberrant axonal projection to the ipsilateral NM from the contralateral NM; in the case of bilateral otocyst removal, each NM innervates the other. The aberrant fibers arise from the contralaterally directed branch of each NM axon near the medial border of the contralateral NL (Fig 8), are present in the NM by E7, form functional glutamatergic synapses, and persist after hatching.[14] The aberrant NM axons go only to the contralateral NM (and not, for example, to adjacent vestibular nuclei that have also been deafferented by otocyst removal) and form a remarkably normal tonotopic array in their new target.[15] Although the aberrant NM-to-NM axons retain the boutonal form and size typical of NM axon terminals in the NL (rather than assuming the large calycine form of cochlear nerve terminals in the NM), the aberrant endings are deeply invaginated by their NM targets and form "hybrid" contacts with features of both normal NM-NL endings and cochlear nerve–NM endings.[16,17] There is good evidence that no aberrant axons other than those from the contralateral NM are present in the NM after otocyst removal.[16] Although it was attractive to speculate that this aberrant projection could account for the survival of 70% of the NM's neurons after otocyst removal, experiments in which the left otocyst and the right rhombic lip (precursor of the NM, NA, NL, and certain other dorsal brain stem nuclei) were surgically destroyed showed that the left NM survived with little apparent reduction in neuronal number.[18]

OTOCYST REMOVAL PREVENTS NORMAL MATURATION OF GLUTAMATE RECEPTOR FUNCTION IN NUCLEUS MAGNOCELLULARIS

We used pharmacophysiologic methods and brain slice preparations to study the normal development of glutamatergic synaptic transmission between the cochlear nerve and the NM.[19] One finding in this study was that the sensitivity of synaptic transmission to blockade by the quinoxalinedione 6-nitro-7-sulfamoyl-benzo(F)quinoxaline-2,3-dione (NBQX; a potent competitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate [AMPA] subtype of glutamate receptor) declined by a factor of 10 between E14 and E21 (ie, the half-maximal inhibitory concentration [IC_{50}] for NBQX increased from 0.27 to 2.7 μmol/L over this period). When similar methods were used to study aberrant NM-to-NM synapses in animals with unilateral otocyst removal,[20] it was found that the immature pattern of greater sensitivity to NBQX is maintained at E21 and for at least 2 weeks after hatching (Fig 9). The failure of the aberrant synapses to undergo normal maturation of NBQX sensitivity suggests that the cochlear nerve axons normally supply some influence necessary for maturation of the AMPA receptors in the NM.

GLUTAMATE RECEPTOR ANTAGONISTS PREVENT DEAFFERENTATION-INDUCED NEURONAL DEATH IN NUCLEUS MAGNOCELLULARIS

All four of the major classes of glutamate receptor (N-methyl-D-aspartate [NMDA], AMPA, kainate, and metabotropic receptors — each with several members) appear to be present on developing chick brain stem auditory neurons. The major focus of our current research is to understand how activation of these functionally distinct receptors affects development of NM and NL neurons. A global approach to

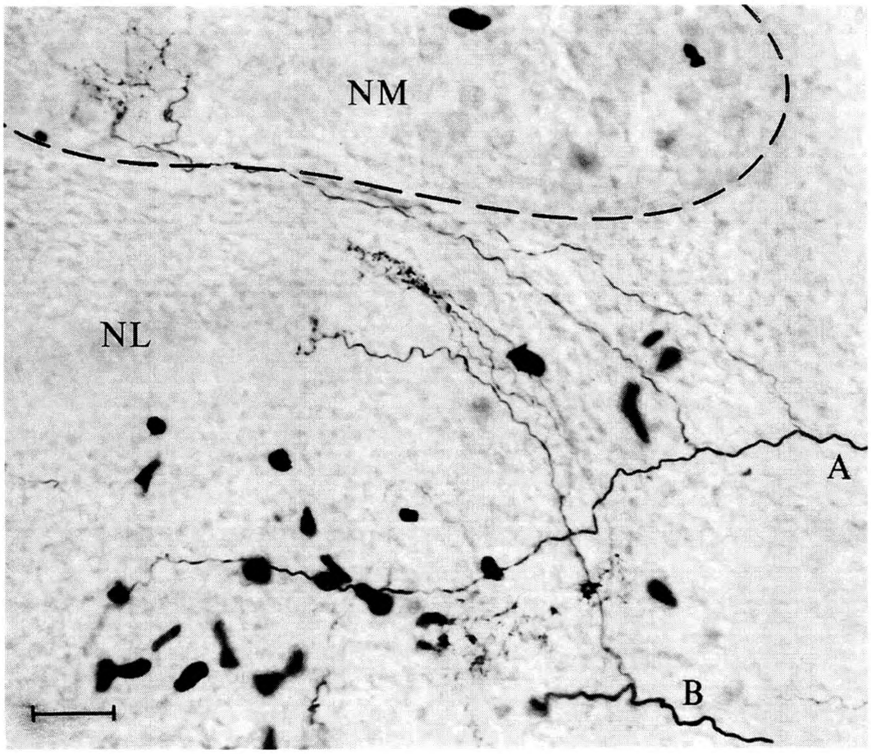


Fig 8. Photomicrograph from E16 animal illustrating anomalous NM-NM connection formed after destruction of otocyst on E3. Small injection of horseradish peroxidase was made at midline to label NM axons. Two axons (A and B) can be seen coursing from midline (right) toward their normal targets in NL. Main branches of both axons pass below NL. Collateral from axon B ascends toward ventral neuropil of NL and there forms normal spray of terminal boutons. Other collaterals bend around medial edge of NL and terminate in dorsal neuropil. Collaterals from axon A take anomalous course to end in sizable arborizations in lateral portion of NM. Scale bar — 50 µm.

this problem has been to administer glutamate receptor agonists and antagonists to developing chick embryos and examine the effects on development. Administration of 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; a quinoxalinedione antagonist of AMPA and kainate receptors) but not RS(±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP; an NMDA antagonist) between E8 and E15 to embryos prevents the normal neuronal death that occurs in the NL between E9 and E17, with little or no effect on the morphology of the brain stem, the auditory nuclei, or individual NL and NM neurons.[21] Treatment with 200 µg/d CNQX between E8 and E15 also prevents the neuronal loss in the NM caused by unilateral otocyst removal.[21] We have recently found that daily administration of 200 µg CNQX for only 3 days (E8 to E10) can also prevent all normal neuronal death in the NL.[22] That this dose of CNQX can suppress spontaneous motility of the embryo for less than 4 hours[22] suggests that drug administered on E8 to E10 produces its survival-promoting effect on NL neurons before the onset of fully functional synapses in NL at E11.[23] We hypothesize that the doses of CNQX that are effective in preventing neuronal death maintain some key physiological parameter (eg, cytosolic calcium concentration or neurotrophin concentration) at a level consistent with enhanced survival relative to normal activity patterns (in the case of normal neuronal death in the NL) or greatly reduced activity (in the case of otocyst removal and the NM). Since at least one quinoxalinedione has been in clinical trials as a stroke treatment, these compounds (or other glutamate receptor antagonists) may offer a novel approach to preventing neuronal loss in the central auditory system after sensorineural deafness.

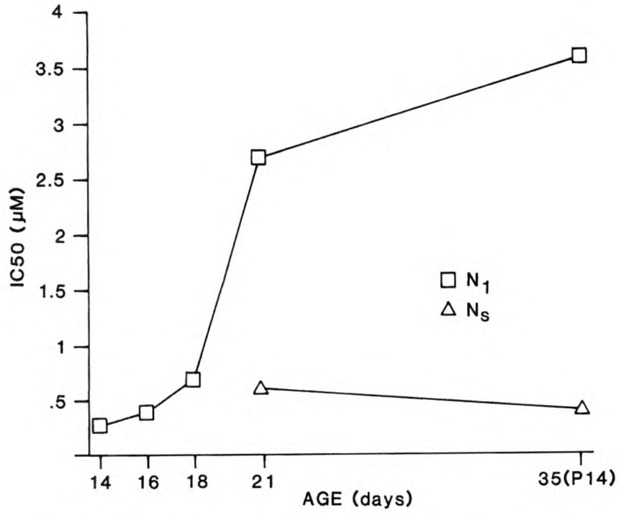


Fig 9. Graph showing that aberrant NM-NM synapses maintain pharmacologically immature glutamate receptors. Developmental changes in potency of glutamate receptor antagonist NBQX in inhibiting synaptic transmission at normal cochlear nerve synapses in NM (N1) and at aberrant NM synapses formed in contralateral NM after otocyst removal (Ns) are summarized. Half-maximal inhibitory concentration (IC50) of NBQX on N1 increases about 13-fold between E14 and P14, but aberrant synapses maintain low IC50 and show no change through 2 weeks after hatching (P14). Each point represents mean of three or more independent replications.

ACKNOWLEDGMENTS — I am grateful to John Conlee, Sarvjit Gill, David Hughes, Hunter Jackson, Edwin Rubel, Derek Solum, Dwan Taylor, and Ning Zhou for their contributions to the studies reviewed above.

REFERENCES

1. Arnos KS. Hereditary hearing loss. N Engl J Med 1994; 331:425-31.

2. Jacobson M. Developmental neurobiology. 3rd ed. New York, NY: Plenum Press, 1991.

3. Rubel EW, Parks TN. Organization and development of the avian brain-stem auditory system. In: Edelman GM, Gall WE, Cowan WM, eds. Auditory function: neurobiological bases of hearing. New York, NY: J Wiley, 1988:3-92.

4. Parks TN. Afferent influences on the development of the brain stem auditory nuclei of the chicken: otocyst ablation. J Comp Neurol 1979;183:665-77.

5. Kerr LM, Ostapoff EM, Rubel EW. Influence of acoustic experience on the ontogeny of frequency generalization gradients in the chicken. J Exp Psychol Anim Behav 1979;5:97-115.

6. Tucci DL, Rubel EW. Afferent influences on brain stem auditory nuclei of the chicken: effects of conductive and sensorineural hearing loss on n. magnocellularis. J Comp Neurol 1985; 238:371-81.

7. Jackson H, Parks TN. Functional synapse elimination in the developing avian cochlear nucleus with simultaneous reduction in cochlear nerve axon branching. J Neurosci 1982;2:1736-43.

8. Parks TN, Jackson H. A developmental gradient of dendritic loss in the avian cochlear nucleus occurring independently of primary afferents. J Comp Neurol 1984;227:459-66.

9. Conlee JW, Parks TN. Late appearance and deprivation-sensitive growth of permanent dendrites in the avian cochlear nucleus (n. magnocellularis). J Comp Neurol 1983;217:216-26.

10. Conlee JW, Parks TN. Age- and position-dependent effects of monaural acoustic deprivation in nucleus magnocellularis of the chicken. J Comp Neurol 1981;202:373-84.

11. Smith ZDJ. Organization and development of the avian brain stem auditory nuclei of the chicken: dendritic development in n. laminaris. J Comp Neurol 1981;203:309-33.

12. Parks TN. Changes in the length and organization in nucleus laminaris dendrites after unilateral otocyst ablation in chick embryos. J Comp Neurol 1981;202:47-57.

13. Parks TN, Gill SS, Jackson H. Experience-independent development of dendritic organization in the avian nucleus laminaris. J Comp Neurol 1987;260:312-9.

14. Jackson H, Parks TN. Induction of aberrant functional afferents to the chick cochlear nucleus. J Comp Neurol 1988; 271:106-14.

15. Lippe WR, Fuhrmann DS, Yang W, Rubel EW. Aberrant projection induced by otocyst removal maintains normal tonotopic organization in the chick cochlear nucleus. J Neurosci 1992; 12:962-9.

16. Parks TN, Taylor DA, Jackson H. Adaptations of synaptic form in an aberrant projection to the avian cochlear nucleus. J Neurosci 1990;10:975-84.

17. Parks TN, Taylor DA. Altered distribution of synaptic densities at aberrant synapses in the chick cochlear nucleus. Neurosci Lett 1993;150:117-21.

18. Parks TN, Gill SS. Afferent regulation of development in the avian nuclei laminaris and magnocellularis studied by destruction of the contralateral rhombic lip [Abstract]. Assoc Res Otolaryngol Abstr 1990:64-5.

19. Zhou N, Parks TN. Developmental changes in the effects of drugs acting at NMDA or non-NMDA receptors on synaptic transmission in the chick cochlear nucleus (n. magnocellularis). Dev Brain Res 1992;67:145-52.

20. Zhou N, Parks TN. Maintenance of pharmacologically-immature glutamate receptors by aberrant synapses in the chick cochlear nucleus. Brain Res 1993;628:149-56.

21. Parks TN, Solum D, Zhou N. Reduction of normal and deafferentation-induced neuronal death in developing chick brainstem auditory nuclei by in ovo treatment with AMPA/kainate receptor antagonists [Abstracts]. Assoc Res Otolaryngol Abstr 1995.

22. Solum D, Hughes D, Parks TN. Periodic blockade of AMPA/kainate receptors before the onset of synaptic transmission enhances neuronal survival in the chick brainstem auditory system [Abstract]. Soc Neurosci Abstr 1996:22.

23. Jackson H, Hackett JT, Rubel EW. Organization and development of brain stem auditory nuclei in the chick: ontogeny of postsynaptic responses. J Comp Neurol 1982;210:80-6.

Ann Otol Rhinol Laryngol 106:1997

ROLES OF GABAERGIC INHIBITION FOR THE BINAURAL PROCESSING OF MULTIPLE SOUND SOURCES IN THE INFERIOR COLLICULUS

GEORGE D. POLLAK, PHD
AUSTIN, TEXAS

This review explores the question of how spike trains that originate from lower auditory nuclei interact in the inferior colliculus to produce an output that synthesizes the information from all these sources. The focus is on the processing of interaural intensity disparities, the cues animals use to localize high-frequency sounds, and the roles of the lateral superior olives and the dorsal nucleus of the lateral lemniscus (DNLL) in shaping the binaural properties of their targets in the inferior colliculus. The main points advanced in this review are 1) that the DNLL shapes the binaural properties of many inferior collicular neurons, 2) that the inhibitory inputs to the DNLL allow it to act as a switch that can be turned on or off with appropriate acoustic stimulation, and 3) that when two or more stimuli are presented, each from a different region of space, the first stimulus can switch the DNLL to its off position. The consequence of the initial stimulus is that stimuli that follow shortly thereafter cannot activate the DNLL, and thus the binaural properties of those collicular cells that receive inhibition from the DNLL are changed. The implications of this switching action are that the location of the initial signal is coded appropriately, whereas the coding of the location of the signal or signals that follow the initial signal is smeared, and consequently, those following signals cannot be accurately localized. In short, it is proposed that the DNLL plays a pivotal role in the way the locations of multiple sound sources are coded by the auditory system.

KEY WORDS — binaural processing, dorsal nucleus of lateral lemniscus, GABAergic inhibition, inferior colliculus, sound localization.

INTRODUCTION

The inferior colliculus is not only centrally important for auditory processing, but it is also a unique structure that has no counterpart either in the auditory system or in any of the other sensory systems. There are two principal features that make it unique. The first is that the vast majority of lower auditory nuclei, whether monaural or binaural, converge at a common destination in its central nucleus (Fig 1) (reviewed by Aitkin[1] and by Oliver and Huerta[2]). This feature

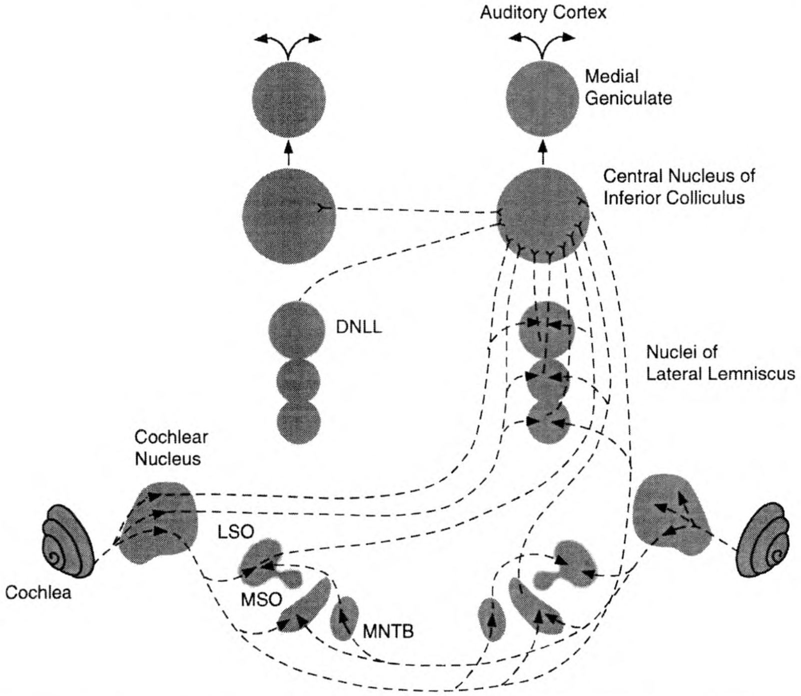


Fig 1. Schematic diagram of ascending auditory system that illustrates massive convergence at inferior colliculus. DNLL — dorsal nucleus of lateral lemniscus, LSO — lateral superior olivary nucleus, MSO — medial superior olivary nucleus, MNTB — medial nucleus of trapezoid body.

From the Department of Zoology, University of Texas at Austin, Austin, Texas. Supported by a grant from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders (DC20068). This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Texas.

CORRESPONDENCE — George D. Pollak, PhD, Dept of Zoology, University of Texas at Austin, Austin, TX 78712.

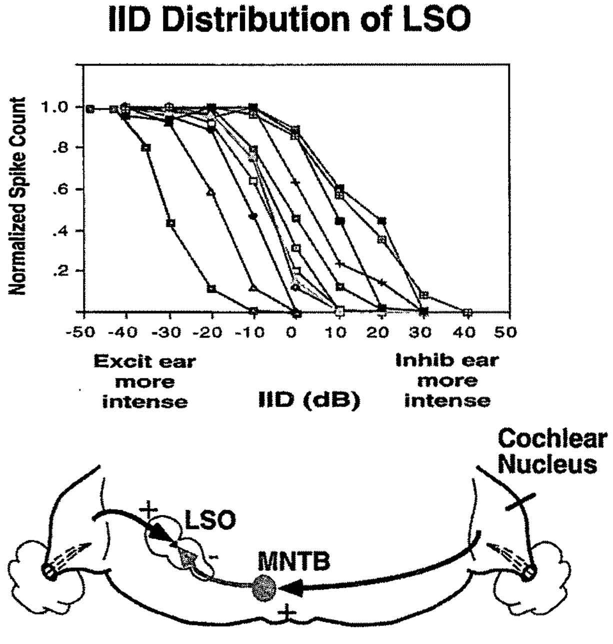


Fig 2. Variety of interaural intensity disparity (IID) functions obtained from LSO of mustache bat. Each function was obtained by driving LSO cell with sound of fixed intensity (15 to 20 dB above threshold) at ipsilateral ear and simultaneously presenting sounds of progressively higher intensities at contralateral ear. Notice that each unit is completely inhibited at particular IID, which varies among population.

alone illustrates the importance of the inferior colliculus for processing acoustic information. The second feature is that the projections not only provide excitatory innervation, but inhibitory innervation as well (Fig 2). The inhibitory innervation is both glycinergic and GABAergic (GABA = γ-aminobutyric acid) and is as large as, if not larger than, the excitatory innervation.[3-6]

The inferior colliculus, however, is in many ways an enigma. On the one hand, judging from single unit recordings, the response properties of collicular neurons are very similar to those of the lower nuclei from which they receive their innervation, and thus their response properties may be, for the most part, a reflection of the particular lower nuclei that target the collicular cell in question. The similarities, then, suggest that there may be much less processing in the inferior colliculus than one might expect from its innervation. On the other hand, given the enormous convergence of excitatory and inhibitory inputs, it is difficult to imagine that there is not a corresponding degree of processing, and hence substantial transformations of response features.

This enigmatic quality of the inferior colliculus frames one of the central questions of auditory neuroscience: *How is it that spike trains relayed via many parallel routes interact in the inferior colliculus to produce an output that synthesizes the information from all of these sources?* It is this question that this chapter is concerned with. Specifically, I will describe some recent studies on the mustache bat that focus on the roles of the pathways concerned with the processing of interaural intensity disparities (IIDs), the cues animals use to localize high-frequency sounds.[7] Although these animals exhibit highly specialized acoustic behaviors, their brain stem auditory system has a physiology similar to that of other, less specialized mammals, as well as comparable nuclei, cell types, connections, and neurochemistry.[6,8,9] Consequently, the results of the studies described below almost surely are reflective of general features of the mammalian auditory system. The results pertain to two specific issues. The first is the influences of the projections of the ipsilateral and contralateral lateral superior olivary nuclei (LSOs) on their targets in the dorsal nucleus of the lateral lemniscus (DNLL). The second is the influences that the projections from the

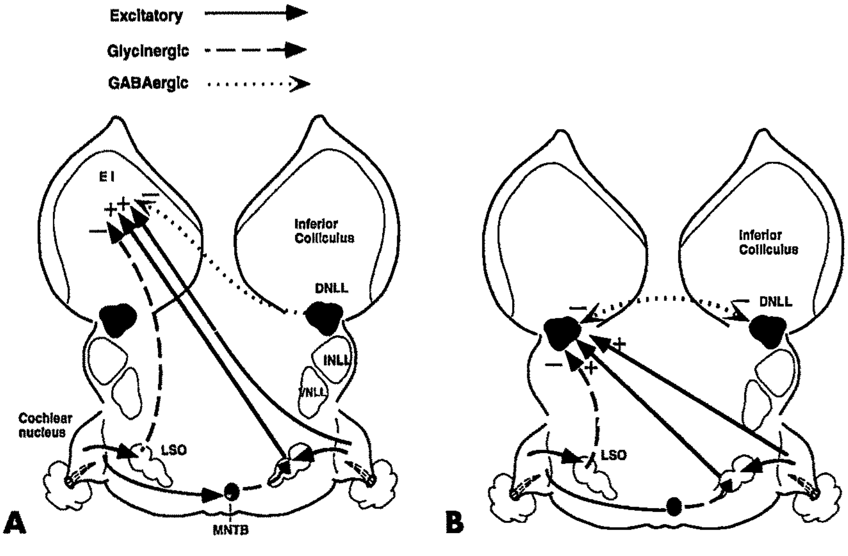


Fig 3. Schematic diagram showing some of major projections to A) region of inferior colliculus dominated by excitatory-inhibitory (EI) neurons and to B) DNLL. Significant features are that both inferior colliculus and DNLL receive strong projections from both ipsilateral and contralateral LSOs, as well as from contralateral DNLL. In addition, inferior colliculus and DNLL also receive innervation from lower centers that are monaural. Projection shown from cochlear nucleus is shown for didactic purposes and is only one of several possible sources of neurons with monaural properties. INLL — intermediate nucleus of lateral lemniscus, VNLL — ventral nucleus of lateral lemniscus.

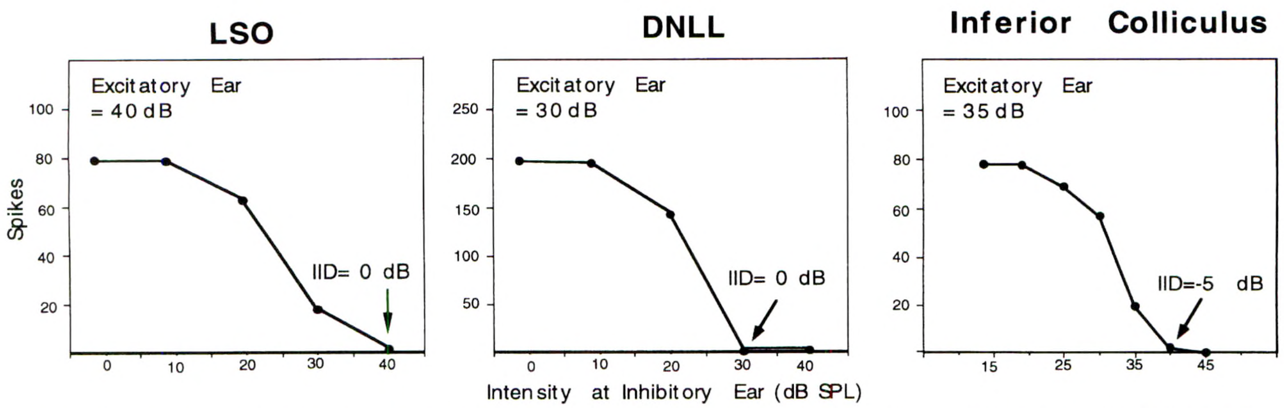


Fig 4. Representative IID functions from LSO, DNLL, and inferior colliculus of mustache bat that illustrate similar binaural properties in each nucleus. SPL — sound pressure level.

LSO and DNLL have for shaping the binaural response properties of their targets in the inferior colliculus, and the roles these projections play in coding for the locations of sound sources.

PATHWAYS IN BRAIN STEM AUDITORY SYSTEM THAT PROCESS INTERAURAL INTENSITY DISPARITIES

The IIDs are processed in the brain stem auditory system through a series of monaural and binaural pathways that converge in the inferior colliculus. As shown in Fig 2, this IID pathway begins in the LSO, where the coded intensities from the two ears are initially "compared."[10,11] The comparison is a subtractive process, whereby signals from the ipsilateral ear excite, and signals from the contralateral ear inhibit, LSO cells.[12-15] Such neurons are referred to as excitatory-inhibitory (EI) neurons. Almost all LSO cells express this property and thus are EI.

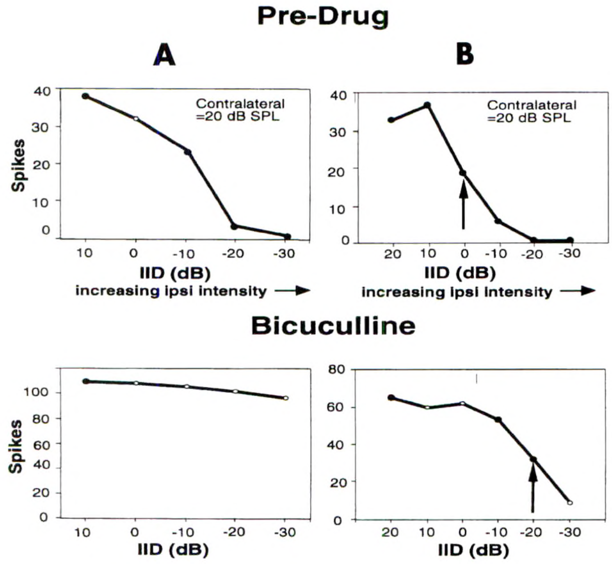


Fig 5. Different effects of blocking GABAergic inhibition on IID functions of two neurons in inferior colliculus of mustache bat. A) Blocking GABAergic inhibition eliminated ipsilaterally evoked inhibition and transformed it into monaural neuron. B) Blocking GABAergic inhibition had little effect on degree of ipsilaterally evoked inhibition. Rather, it shifted IID sensitivity of cell, which required more intense ipsilateral signal to achieve same degree of spike suppression than was required before GABAergic inhibition was blocked. Arrows indicate 50% points on each function, ie, ipsilateral intensity that reduced spike count evoked by contralateral signal by 50%.

The processing of the IIDs by EI cells is commonly evaluated by generating an IID function (Fig 2, top panel). The function is generated by presenting a sound of fixed intensity to the excitatory (ipsilateral) ear, which evokes a certain discharge rate in the LSO neuron being studied. A sound is then presented simultaneously to the inhibitory (contralateral) ear at progressively higher intensities. When sound at the inhibitory ear reaches a certain level, and thus exceeds the threshold for evoking spikes from that ear, the activity inhibits the excitation from the other ear, thereby suppressing discharges in the binaural neuron. With further intensity increases at the inhibitory ear, the spikes evoked by the sound at the excitatory ear can be completely suppressed. The net effect of ipsilaterally evoked inhibition is simply to limit the regions of space from which acoustic stimuli will elicit discharges.[16,17]

The principal feature that differs among the population of LSO cells is that each cell is completely inhibited at a different IID (Fig 2, top panel), as found by Sanes and Rubel[14] and Pollak (unpublished observations). Some LSO cells are inhibited by sounds in the ipsilateral acoustic hemifield, which generate IIDs that favor the excitatory ear, while others are inhibited by sounds in progressively more contralateral regions of acoustic space, each of which generate IIDs that favor more greatly the inhibitory ear. Thus, the IID generated by a sound source from a particular region of space affects the entire LSO population, and it is the pattern of activity of the ensemble that codes the IID of the sound, and thus its location in space.[8,18,19]

The main projections from the LSO become com-

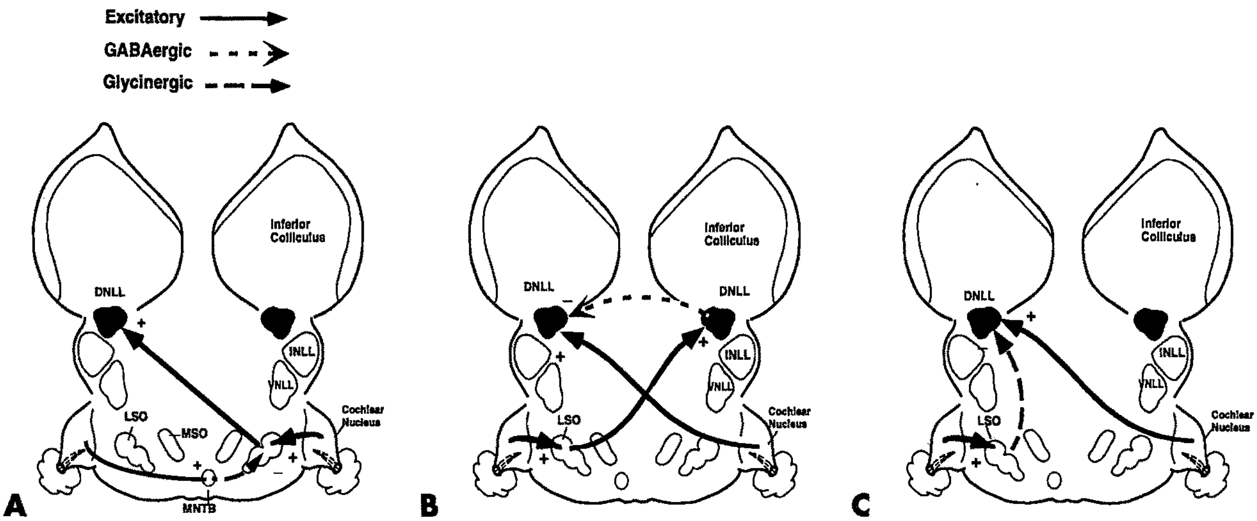


Fig 6. Circuit diagrams showing three alternative ways in which EI properties could be created in DNLL. A) EI property is originally created in contralateral LSO and imposed upon DNLL via excitatory projection from contralateral LSO. In this scenario, blocking GABAergic or glycinergic inhibition at DNLL should have no effect on binaural properties of DNLL cell from which we are recording. B) EI property is created in DNLL from excitatory projection that originates in lower monaural nucleus and GABAergic projection from opposite DNLL. In this scenario, blocking GABAergic inhibition at DNLL should make cell monaural, while blocking glycinergic inhibition should have no effect on binaural property of DNLL cell. C) Binaural property is created in DNLL by monaural projection from lower nucleus and glycinergic projection from ipsilateral LSO. In this case, blocking glycinergic inhibition should make cell monaural, while blocking GABAergic inhibition should have no effect on binaural properties.

plex, because each LSO sends *bilateral projections* to two higher regions, the DNLL and the inferior colliculus (Fig 3).[20-23] The potential ways in which the LSO and DNLL can impact their targets in the inferior colliculus can be understood by considering both the connections and the neurotransmitters of the projection neurons. The crossed projections from the LSO to the contralateral DNLL and inferior colliculus are excitatory, and are probably glutamatergic.[3,24,25] In contrast, the uncrossed projections from the LSO to the ipsilateral DNLL and inferior colliculus are largely glycinergic, and thus inhibitory, although some ipsilateral projections may also be excitatory. The DNLL, however, is dominated by GABAergic neurons.[6,26-28] Thus, its projections are largely inhibitory to their targets in the opposite DNLL and to their targets in both the ipsilateral and contralateral inferior colliculi.

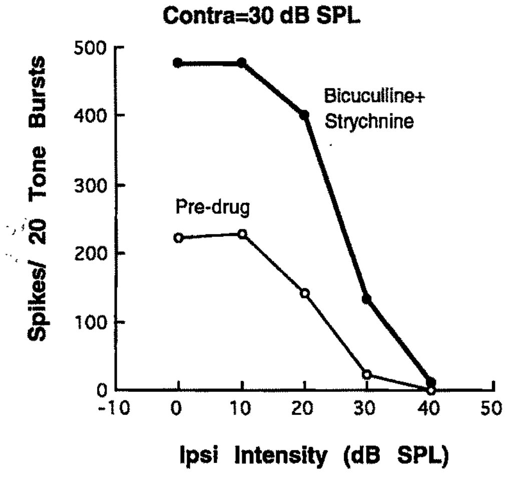


Fig 7. Effects of blocking GABAergic inhibition with bicuculline and glycinergic inhibition with strychnine on spike suppression evoked by stimulation of ipsilateral ear of representative DNLL neuron. Interaural intensity functions are shown both before (predrug) and during application of bicuculline and strychnine. In both cases, contralateral stimulus was 20-millisecond tone burst whose intensity was held constant at 30 dB SPL. Graphs show effects of increasing intensities at ipsilateral ear on constant excitatory drive evoked by 30-dB SPL signal at contralateral ear. Application of bicuculline and strychnine had no effect on spike suppression with increasing ipsilateral sound intensities. Only effect of bicuculline and strychnine was to increase spike count evoked by contralateral sound.

COMMON EI PROPERTIES THAT DOMINATE LSO, DNLL, AND INFERIOR COLLICULUS RAISE A CENTRAL QUESTION

While the EI pathway is complex, the binaural properties of the neurons in each of the nuclei are remarkably similar (Fig 4).[12,17,19,29-31] Not only is each region dominated by EI neurons, but the distributions of IID sensitivities are also similar among the populations (not shown). The common features among the three nuclei represent a specific example of the central question described previously. That question can now be rephrased to ask, *What is the functional significance of such a complex pathway, when the end result is binaural properties of neurons in the inferior colliculus that are so similar to those in the LSO?*

Recent studies have provided some answers to this

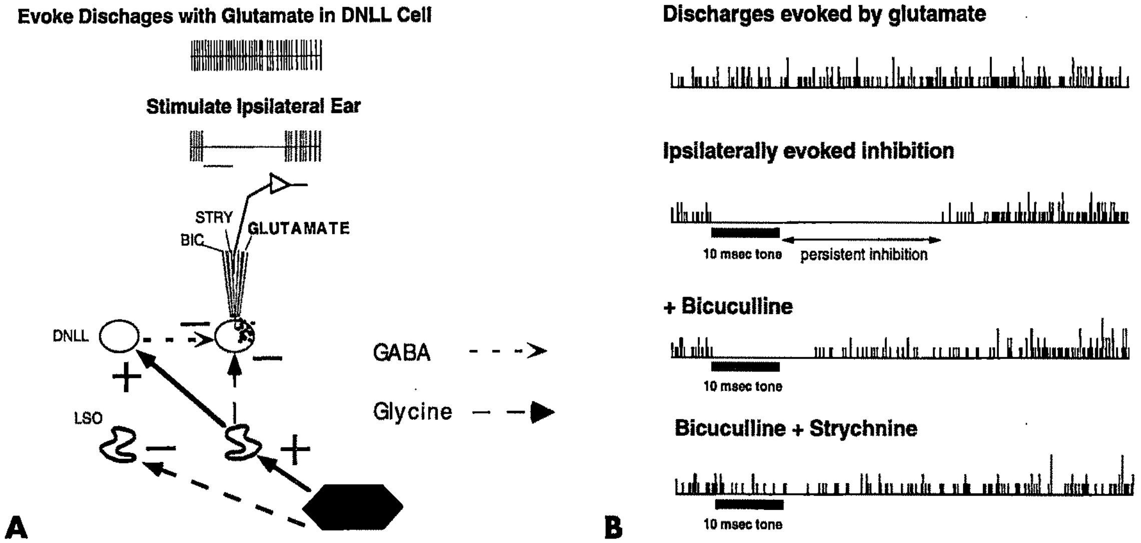


Fig 8. A) Schematic showing circuitry activated by stimulation of ipsilateral ear and why that circuitry showed discharges evoked by iontophoretic application of glutamate on DNLL cells. B) Actual records of glutamate-evoked discharges in DNLL. Records from top show 1) discharges in absence of acoustic stimulation; 2) long-lasting inhibition of glutamate-evoked spikes by ipsilateral stimulation; 3) abolishment of later portions of ipsilaterally evoked inhibition by blocking GABAergic inhibition with bicuculline; and 4) complete abolishment of ipsilaterally evoked inhibition by blocking both GABAergic and glycinergic inhibition.

question.[32-34] They suggest that while the binaural properties of the nuclei in the EI pathway are superficially similar, numerous transformations of binaural properties occur in the inferior colliculus. Those studies have shown that the DNLL contralateral to the inferior colliculus plays a pivotal role, since it shapes the binaural response features of many EI neurons in the inferior colliculus through its inhibitory influences.

CONTRALATERAL DNLL HAS TWO MAJOR INFLUENCES ON ITS TARGETS IN INFERIOR COLLICULUS

The consequences of the inhibitory projections from the DNLL are fairly straightforward. I illustrate two of the principal influences from studies that evaluated the changes in binaural properties of EI neurons in the inferior colliculus when GABAergic inhibition was blocked by the iontophoretic application of bicuculline, an antagonist specific for GABAA receptors.[16,34]

The first effect is that blocking GABAergic inhibition substantially reduces or eliminates the ipsilaterally evoked inhibition in about 40% of the inferior colliculus cells (Fig 5A). These cells were transformed from strongly inhibited EI cells into weakly inhibited cells or into monaural cells. This suggests

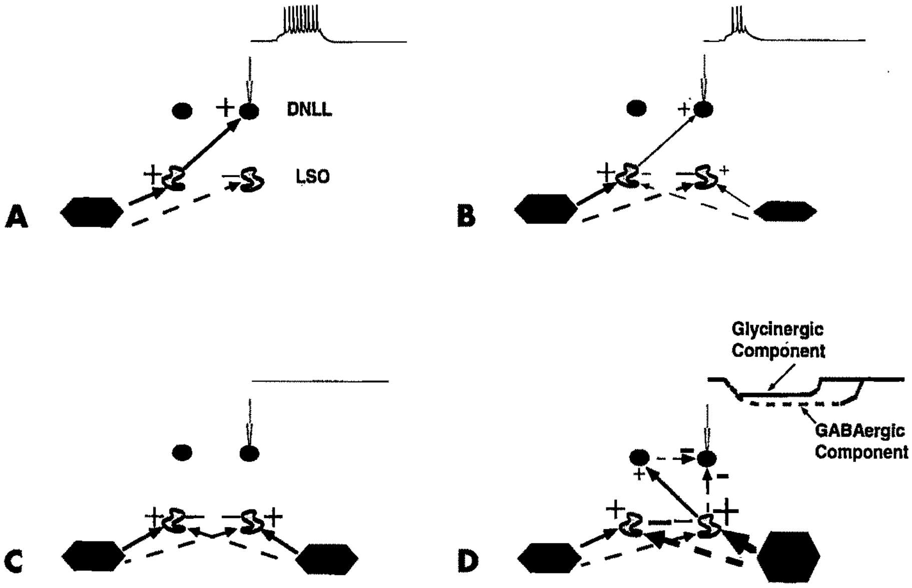


Fig 9. Circuit diagrams showing push-pull effects of binaural stimulation on LSOs and influences of LSOs on their targets in DNLL. Each panel shows hypothetical intracellular recording from DNLL cell in response to A) monaural and B-D) binaural stimulation. See text for further explanation.

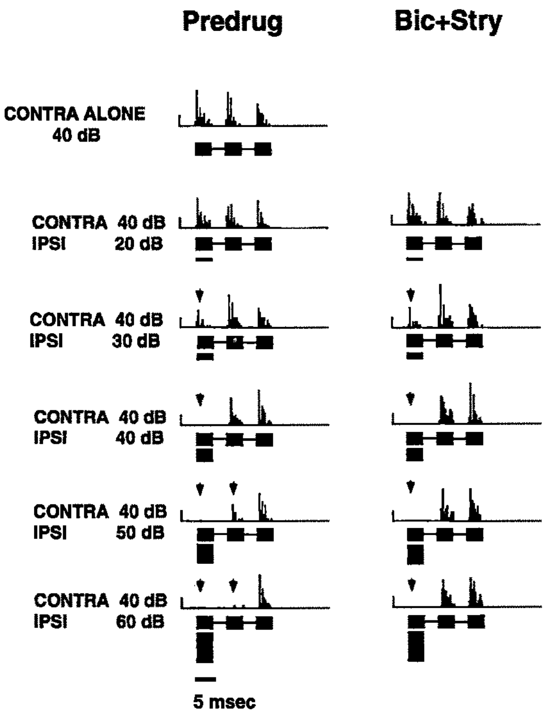


Fig 10. Effects of initial binaural tone burst on discharges evoked by two monaural tone bursts that followed shortly thereafter. Left panel shows responses prior to application of bicuculline and strychnine (predrug). Top record shows three monaural tone bursts, each at 40 dB SPL, all evoking vigorous discharges from DNLL cell. Each record below then shows effects of initial binaural signal with progressively increasing interaural intensity disparities on responses to two conditions, following monaural signals. Contralateral intensity was fixed at 40 dB SPL for three tone bursts. As ipsilateral intensity of first sound increased, discharges to first sound were initially suppressed (arrows). With additional intensity increments at ipsilateral ear, discharges to second sound were reduced and then almost completely suppressed (second arrows). Blocking GABAergic and glycinergic inhibition rescued responses to second, monaural tone burst, but did not rescue response to first, binaural tone burst. Three tone bursts had durations of 5 milliseconds and were separated by 5-millisecond intervals.

that the target cell in the inferior colliculus received an excitatory projection from a lower monaural nucleus, which drove the cell, and an inhibitory projection from the contralateral DNLL. The inhibitory projection from the DNLL was most likely responsible for the ipsilaterally evoked inhibition and, thus, for generating the binaural or EI property of the cell.

The second effect of the DNLL, found in about 30% of inferior colliculus neurons, is that it changes the IID that causes spike suppression at some criterion in the collicular cell (Fig 5B). In other words, blocking GABAergic inhibition causes a shift in the cell's IID sensitivity, although it has little effect on the degree of spike suppression (the cells are still strongly suppressed at some IID).

THE ABOVE RESULTS ANSWER ONE QUESTION BUT RAISE ANOTHER

While the results cited above have revealed some of the influences of the DNLL on their targets in the inferior colliculus, they are functionally unsatisfying. They simply show that the EI properties of some neurons are *not* formed in the LSO, but rather, in the inferior colliculus itself, and that the IID sensitivities of other units, while initially formed in the LSO, are further modified in the inferior colliculus. The puzzling issue here is that the population of LSO neurons have the same EI properties and the same range of IID sensitivities as those seen in both the DNLL and inferior colliculus. Thus, while the previous studies have provided insights into what the influences of DNLL projections are in the inferior colliculus, they provide no insights into why EI properties are formed and IID sensitivities further modified in the inferior colliculus. Those results, then, simply force us to recast the question posed previously. The question now becomes, *What are the functional consequences of recreating response properties in the inferior colliculus that have already been created in full form in the LSO?* I defer addressing that question for the moment and, rather, focus attention on the DNLL, because understanding the physiology of the DNLL is one of the keys for understanding why the projections from the DNLL recreate LSO-like response properties in the inferior colliculus.

FORMATION OF EI PROPERTIES IN DNLL

I now turn to the DNLL, a nucleus whose physiology was, until recently, virtually ignored by auditory neuroscientists. This lack of information about the DNLL prompted my colleagues and me to conduct a series of studies on the DNLL, in which we evaluated its discharge properties with single unit recordings[30,35] and then asked what role the projections to the DNLL play in shaping the binaural properties of its neuronal population.[36,37] The results of these experiments are surprising and suggest a number of more complex influences that the DNLL may have on its targets in the inferior colliculus.

The logic of DNLL experiments is similar to that of pharmacologic experiments that we conducted on the inferior colliculus, and follows directly from the projections to the DNLL. Those projections suggest that the EI properties of DNLL neurons could be produced in three ways, as shown in Fig 6. The first way is by a direct, excitatory projection from the contralateral LSO, the nucleus in which the EI properties are initially formed. The second is through an excitatory, monaural projection from the contralateral ear, which in turn would be inhibited by a

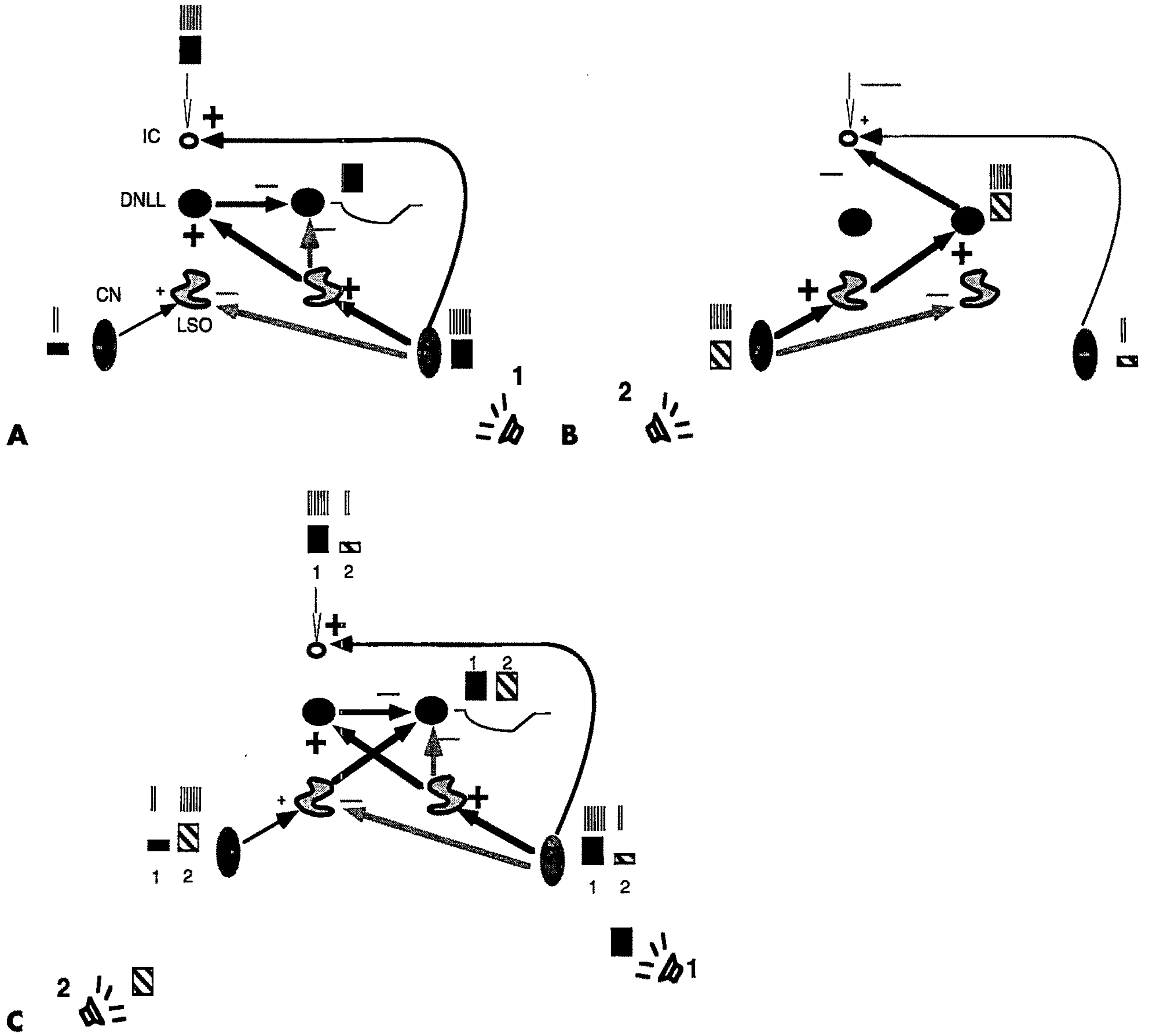


Fig 11. Representation of how spatial selectivity of neuron in inferior colliculus could be changed by order of two sounds received from different regions of space. We assume binaural properties of neuron in inferior colliculus are formed by excitatory monaural projection driven by contralateral ear and inhibitory projection from DNLL contralateral to EI collicular cell (we refer to that DNLL as projection DNLL to distinguish it from DNLL ipsilateral to EI cell in inferior colliculus). A) Illustrates projections to collicular cell when tone burst is presented from contralateral sound field. This sound is intense at contralateral ear and weaker at ipsilateral ear due to shadowing. Sound generates strong excitatory drive in monaural projection, shown here diagrammatically as originating in cochlear nucleus, and thus drives collicular cell. It also strongly drives LSO contralateral to collicular cell, which provides strong inhibition to projection DNLL, resulting in persistent inhibition. B) Shows that sound presented from ipsilateral sound field provides weak excitation to contralateral cochlear nucleus (due to shadowing) and thus weak excitatory drive to collicular cell. However, sound strongly drives ipsilateral LSO, which then drives projection DNLL. Projection DNLL then imparts strong inhibition to collicular cell that overrides weaker excitation. C) Shows effects on these circuits on collicular cell when tone burst is first presented from contralateral sound field, followed shortly thereafter by same sound presented from ipsilateral sound field. Discharges evoked by first sound are shown above black boxes, while discharges evoked by second tone burst are shown above open boxes. Key feature under these conditions is that first tone burst generates strong, persistent inhibition in projection DNLL. When tone burst is then presented from ipsilateral sound field few milliseconds later, it weakly stimulates contralateral cochlear nucleus, which provides weak excitatory drive to collicular cell. However, persistent inhibition generated in projection DNLL by first tone burst prevents projection DNLL from responding to second tone burst. Thus, collicular cell now responds both to first tone burst and to second tone burst. In other words, collicular cell now responds to tone burst presented from ipsilateral sound field, whereas collicular cell was completely unresponsive to same tone burst when it was presented alone.

GABAergic projection from the opposite DNLL via the commissure of Probst. The third way is also by an excitatory, monaural projection from the contralateral ear, such as from the cochlear nucleus, but in this case the excitation would be inhibited by a glycinergic projection from the ipsilateral LSO. The rationale here is that neurons in the contralateral DNLL and ipsilateral LSO are excited by stimulation of the ipsilateral ear (Fig 6B,C) and thus are in a favorable position to provide a potent inhibitory influence on their targets in the DNLL, thereby creating the EI property of the DNLL cell.

The results of the pharmacologic experiments showed that the inhibition evoked by ipsilateral stimulation was unaffected by blocking either glycinergic or GABAergic inhibition in the vast majority of DNLL neurons (Fig 7).[36,37] It would appear, therefore, that the EI properties of DNLL neurons are created in the LSO and that property is then imposed on the DNLL via the crossed excitatory projection from the LSO shown in Fig 6A. This is unlike the inferior colliculus, in which the binaural properties are strongly influenced by inhibitory projections from the contralateral DNLL and by the glycinergic projections from the ipsilateral LSO. (The influences of the glycinergic projections were not mentioned previously, but are reported in Klug et al.[38]) And yet the DNLL, like the inferior colliculus, also receives strong inhibitory projections from the ipsilateral LSO and from the contralateral DNLL, both of which are evoked by stimulation of the ipsilateral ear (Fig 6B,C).

While the inhibition of spikes with binaural stimulation occurs in the LSO, ipsilaterally evoked inhibition can also be demonstrated at the DNLL.[36,37] The ipsilateral inhibition can be revealed by evoking background discharges in DNLL cells by iontophoresing the excitatory transmitter, glutamate, and then presenting sound to the ipsilateral ear (Fig 8A). Under these conditions, ipsilateral stimulation suppressed the glutamate-evoked discharges. Of particular importance is that not only were the glutamate spikes suppressed by ipsilateral stimulation, they were suppressed for a period that far outlasted the duration of the tone burst that evoked the inhibition (Fig 8B). I shall refer to the period of inhibition that extended beyond the duration of the tone burst as the *period of persistent inhibition*. Furthermore, as required by the circuitry, the ipsilaterally evoked inhibition has both GABAergic and glycinergic components: the later portions of the inhibition of the glutamate-evoked spikes could be eliminated by applying the GABA A receptor blocker bicuculline, while the earlier portion of the inhibition could be eliminated by the glycine receptor blocker strychnine. The entire inhibition could be blocked when bicuculline and strychnine were applied simultaneously (Fig 8B).

Taken together, these results appear paradoxical. The apparent paradox is that the ipsilaterally evoked suppression of sound-evoked spikes in DNLL cells is a reflection of inhibition that actually occurs in the LSO, but the same DNLL cells are also receiving a long-lasting GABAergic and glycinergic inhibition evoked by ipsilateral stimulation that does not contribute to the spike suppression with binaural stimulation. The paradox can be reconciled by considering the push-pull influences of the two LSOs.[36] These influences are illustrated in Fig 9, which shows the effects of the projections from a small group of cells in each LSO on a target cell in the DNLL. For simplicity, we consider the effects at the DNLL of increasing the intensity at the ear ipsilateral to the DNLL upon a constant excitatory drive evoked by a fixed intensity at the contralateral ear. The principal feature of this circuit is that sound intensity at the contralateral ear excites the cells in the LSO contralateral to the DNLL and inhibits the cells in the LSO ipsilateral to the DNLL (Fig 9A). When sound is more intense at the contralateral ear than the ipsilateral ear, the cells in the LSO contralateral to the DNLL are driven and provide an excitatory drive to the target DNLL cell, while the cells in the LSO ipsilateral to the DNLL are inhibited (Fig 9B). At some higher ipsilateral intensity, a balance is reached in which the influences of the two ears are equal in the cell groups of both LSOs (Fig 9C). Under this condition, the excitation and inhibition on the cell groups in both LSOs cancel each other, and neither LSO influences its target in the DNLL. At this IID, the DNLL cell is receiving neither excitation nor inhibition, and its spike count falls to zero. The key event occurs when the interaural intensity balance shifts to favor the ipsilateral ear (Fig 9D). Now, the inhibition on the cell group in the LSO contralateral to the DNLL outweighs the excitation, whereas excitation outweighs inhibition in the cell group of the ipsilateral LSO. With an IID that favors the ipsilateral ear, the cells in the LSO ipsilateral to the DNLL are driven, and the driven activity has two principal effects (Fig 9D). The first is that it provides a glycinergic inhibition to the ipsilateral DNLL, thereby evoking a short-latency inhibitory postsynaptic potential (IPSP). The second effect is to provide an excitatory input to the DNLL on the opposite side, thereby driving those DNLL cells. These DNLL cells then provide a GABAergic input, via the commissure of Probst, to the DNLL on the other side, ie, the DNLL from which we were recording.

There are two significant features of the above hypothesis: 1) the duration of those inhibitory events outlasts the duration of the ipsilateral signal that evoked them, and 2) the two inhibitory effects at the DNLL are only evoked by IIDs larger than those that completely suppress the cells in the contralateral LSO. Thus, the inhibition from the glycinergic and GABAergic projections is imposed on a DNLL cell that is receiving no excitation, but rather, whose membrane potential is at a resting value.

THE HYPOTHESIS MAKES PREDICTIONS THAT CAN BE TESTED

The above hypothesis is consistent with the circuitry and transmitters used by that circuitry, as well as with our results from the DNLL studies. It therefore provides a viable mechanism for explaining the results we obtained. However, it made us wonder what functional significance accrues to providing long-lasting inhibitory inputs to a cell whose activity has already been fully suppressed.

If one thinks about a situation in which the animal receives more than one signal, then the activity generated by the circuit could be functionally relevant. The argument is that if a sound emanates from a region of space that generates a much more intense sound at the ipsilateral than the contralateral ear (as in Fig 9D), the persistent inhibition would influence the DNLL neuron's ability to respond to subsequent or trailing stimuli that would normally be excitatory to that neuron (such as the signal in Fig 9B). In short, we proposed that the functional significance of the persistent inhibition evoked by stimulation of the ipsilateral ear is to influence the processing by DNLL neurons of multiple sounds that emanate from different regions of space and thus generate different IIDs.[37]

The push-pull hypothesis predicts that a series of stimuli separated by several milliseconds should exhibit a characteristic pattern of response suppression at the DNLL as the IID of the initial stimulus is increased to progressively favor the ipsilateral ear. Specifically, as the ipsilateral intensity increases, it should first suppress completely the discharges evoked by the first signal, since this suppression is caused by inhibition at the contralateral LSO. Further increases in the ipsilateral intensity should then evoke both a glycinergic inhibition from the ipsilateral LSO and a GABAergic inhibition from the opposite DNLL that persists after the initial tone burst has ended. Moreover, the persistent inhibition should lengthen with increasing ipsilateral intensity. As a consequence, the excitation at the DNLL by signals that follow the initial signal should be suppressed if those excitatory events arrive at the DNLL cell during the period of persistent inhibition generated by the first stimulus.

We tested this prediction by presenting three tone bursts of 5 milliseconds' duration to the contralateral (excitatory) ear, with each tone burst separated by a 5-millisecond interval.[36,37] We then made the first stimulus binaural (but kept the two succeeding tone bursts monaural) and progressively increased the ipsilateral intensity of the first tone burst (Fig 10, left panel). The prediction is that as the intensity of the ipsilateral tone burst increases, it should initially suppress the discharges to the first tone burst, which occurs in the LSO, while leaving the responses to the two succeeding, monaural tone bursts unchanged. With further increases in the ipsilateral intensity, the discharges evoked by the subsequent tone bursts should then be inhibited due to the generation of a persistent inhibition at the DNLL. This prediction was confirmed and is illustrated by the DNLL neuron shown in Fig 10.

We next evaluated whether the spike suppression observed for each of the tone bursts was due to an inhibition at the DNLL, or whether the suppression was a reflection of an inhibition that occurred in a lower nucleus. To distinguish between these alternatives, we presented the three-tone paradigm described above and then repeated the stimulus paradigm after blocking GABAergic inhibition with bicuculline, and glycinergic inhibition with strychnine. In each of the neurons that were tested in this way, blocking GABAergic and glycinergic inhibition partially or completely rescued the responses evoked by the second tone bursts (Fig 10, right panel). However, the suppression of the spikes to the first tone burst was never rescued in any of the neurons that we studied. These results confirm the hypothesis that the suppression of spikes evoked by the first binaural signal occurred in the LSO, while the spike suppression of the second signal was due to the persistent inhibition in the DNLL. The spikes evoked by the third signal were not suppressed, presumably because they occurred beyond the period of persistent inhibition.

SOME FUNCTIONAL CONSEQUENCES OF PERSISTENT INHIBITION IN DNLL ON INFERIOR COLLICULUS

These findings suggest that the DNLL plays at least two roles that can differentially shape the spatial properties of its targets in the inferior colliculus. One role is played by the response of the DNLL to an initial sound received at the two ears, and the other role is determined by the response of the DNLL to sounds that follow the initial sound. The distinction between these roles is that for the initial sound, the effects that the DNLL exert on the inferior colliculus depend only upon the absolute intensity and IID of that sound. Stated differently, the DNLL will respond to IIDs generated by the initial signal in the same way whether that signal is the only signal received or if it is the first of several signals that follow closely thereafter. In contrast, the response of the DNLL to a second signal is variable, and is dependent on whether or not the first signal evoked inhibition in the DNLL cell.

I now return to the question posed at the beginning of this chapter concerning the functional significance of the complex projections from the LSO to the DNLL and inferior colliculus, given that the binaural properties of inferior colliculus neurons are so similar to those of the LSO and DNLL. I am led to conclude that the alteration of IID sensitivities and the formation of EI properties in inferior colliculus cells due to the inhibitory influences from the contralateral DNLL are, in themselves, epiphenomena. I say this because the same constellation of properties in the inferior colliculus could be and is achieved even without the DNLL projection, simply through the projections from the contralateral LSO. The features that could *not* be achieved solely through the LSO projection to the inferior colliculus are modifications of binaural properties to trailing signals. Those modifications are a consequence of the inhibitory projections from the DNLL, because their actions on the inferior colliculus to the first signal can be different from those to the second signal. In short, I am arguing that one of the principal consequences of the complex projections of the IID pathway is to influence the processing of multiple sound sources that originate from different regions of space.

The functional consequence of this hypothesis is that since the DNLL activity shapes the receptive fields and thus the spatial selectivities of its targets in the inferior colliculus,[16] changing the activity of the DNLL cell with a preceding signal degrades the spatial selectivities of its targets in the inferior colliculus for the following or trailing signal. An illustration of how this would work is shown in Fig 11 for one type of EI neuron that I showed earlier, one whose binaural properties are formed in the inferior colliculus through the convergence of an excitatory monaural projection driven by the contralateral ear and a GABAergic inhibitory projection from the DNLL driven by stimulation of the ipsilateral ear. But, no matter how the EI properties are initially formed, if a collicular neuron's binaural properties are shaped in any way by inhibitory inputs from the DNLL, then the suppression of those inputs by a preceding signal must change the cell's binaural property and thereby degrade its spatial selectivity for a signal that follows shortly thereafter. Moreover, since the ensemble of EI cells codes the IID of the signal,[8,9,17] and hence its location, degradation of the coding by the ensemble in the inferior colliculus must also degrade the localization of the trailing signal.[37] This general rule is applicable to all binaural collicular neurons that are innervated by the DNLL, and must impact profoundly on the perception of a class of signals that generate IIDs that change with time.

ACKNOWLEDGMENTS — I thank Tom Park, Benedikt Grothe, Gerhard Neuweiler, Lichuan Yang, Pablo Monsivais, and Achim Klug for sharing their thoughts on the auditory system with me, since they influenced my ideas that are expressed in this article.

REFERENCES

1. Aitkin LM. The auditory midbrain: structure and function in the central auditory pathway. Clifton, NJ: Humana, 1985.

2. Oliver DL, Huerta MF. Inferior and superior colliculi. In: Webster DB, Popper AN, Fay RR, eds. The mammalian auditory pathway: neuroanatomy. Vol 1. Berlin, Germany: Springer-Verlag, 1992:168-222.

3. Saint Marie RL, Baker RA. Neurotransmitter specific uptake and retrograde transport of [3H] glycine from the inferior colliculus by ipsilateral projections of the superior olivary complex and nuclei of the lateral lemniscus. Brain Res 1990;524:244-53.

4. Shneiderman A, Oliver DL, Henkel K. The connections of the dorsal nucleus of the lateral lemniscus: an inhibitory parallel pathway in the ascending auditory system? J Comp Neurol 1988; 276:188-208.

5. Shneiderman A, Oliver DL. EM autoradiographic study of the projections from the dorsal nucleus of the lateral lemniscus: a possible source of inhibitory inputs to the inferior colliculus. J Comp Neurol 1989;286:28-47.

6. Winer JA, Larue DT, Pollak GD. GABA and glycine in the central auditory system of the mustache bat: substrates for inhibitory neuronal organization. J Comp Neurol 1995;355:317-53.

7. Erulkar S. Comparative aspects of spatial localization of sound. Physiol Rev 1972;52:237-360.

8. Pollak GD. Adaptations of basic structures and mechanisms in the cochlea and central auditory pathway of the mustache bat. In: Popper A, Fay R, Webster D, eds. Evolutionary biology of the auditory system. Berlin, Germany: Springer-Verlag, 1992:751-78.

9. Pollak GD, Casseday JH. The neural basis of echolocation in bats. Berlin, Germany: Springer, 1989.

10. Cant N, Morest DK. The structural basis for stimulus coding in the cochlear nucleus of the cat. In: Berlin CI, ed. Hearing science. San Diego, Calif: College-Hill, 1984:374-422.

11. Cant NB, Casseday JH. Projections from the anteroventral cochlear nucleus to the lateral and medial superior olivary nucleus. J Comp Neurol 1986;227:63-77.

12. Boudreau JC, Tsuchitani C. Binaural interaction in the cat superior olive S-segment. J Neurophysiol 1968;31:442-54.

13. Moore MJ, Caspary DM. Strychnine blocks binaural inhibition in lateral superior olivary neurons. J Neurosci 1983;3:237-42.

14. Sanes DH, Rubel EW. The ontogeny of inhibition and excitation in the gerbil lateral superior olive. J Neurosci 1988;8: 682-700.

15. Covey E, Vater M, Casseday JH. Binaural properties of single units in the superior olivary complex of the mustached bat. J Neurophysiol 1991;66:1080-93.

16. Park TJ, Pollak GD. Azimuthal receptive fields are shaped by GABAergic inhibition in the inferior colliculus of the mustache bat. J Neurophysiol 1994;72:1080-102.

17. Wenstrup JJ, Fuzessery ZM, Pollak GD. Binaural neurons in the mustache bat's inferior colliculus: II. Determinants of spatial responses among 60 kHz E-I units. J Neurophysiol 1988; 60:1384-404.

18. Reed MC, Blum JJ. A model for the computation and encoding of azimuthal information by the lateral superior olive. J Acoust Soc Am 1990;88:1442-53.

19. Wenstrup JJ, Ross LS, Pollak, GD. Binaural response organization within a frequency-band representation of the inferior colliculus: implications for sound localization. J Neurosci 1986;6:962-73.

20. Brunso-Bechtold JK, Thompson GC, Masterton RB. HRP study of the organization of auditory afferents ascending to the central nucleus of the inferior colliculus in the cat. J Comp Neurol 1981;197:705-22.

21. Glendenning KK, Brunso-Bechtold JK, Thompson GC, Masterton RB. Ascending auditory afferents to the nuclei of the lateral lemniscus. J Comp Neurol 1981;197:673-703.

22. Zook JM, Casseday JH. Convergence of ascending pathways at the inferior colliculus in the mustache bat, *Pteronotus parnellii*. J Comp Neurol 1987;261:347-61.

23. Ross LS, Pollak GD, Zook JM. Origin of ascending projections to an isofrequency region of the mustache bat's inferior colliculus. J Comp Neurol 1988;270:488-505.

24. Saint Marie RL, Ostapoff ME, Morest DK, Wenthold RI. Glycine-immunoreactive projection of the cat lateral superior olive: possible role in midbrain dominance. J Comp Neurol 1989;279:382-96.

25. Glendenning KK, Baker BN, Hutson KA, Masterton RB. Acoustic chiasm V: inhibition and excitation in the ipsilateral and contralateral projections of LSO. J Comp Neurol 1992;319:100-22.

26. Adams JC, Mugniani E. Dorsal nucleus of the lateral lemniscus: a nucleus of GABAergic projection neurons. Brain Res Bull 1984;13:585-90.

27. Vater M, Kössl M, Horn AKE. GAD- and GABA-immunoreactivity in the ascending auditory pathway of horseshoe and mustached bats. J Comp Neurol 1992;325:183-206.

28. Covey E. Response properties of single units in the dorsal nucleus of the lateral lemniscus and paralemniscal zone of an echolocating bat. J Neurophysiol 1993;69:842-59.

29. Brugge JF, Anderson DJ, Aitkin LM. Responses of neurons in the dorsal nucleus of the lateral lemniscus to binaural tonal stimuli. J Neurophysiol 1970;33:441-58.

30. Markovitz NS, Pollak GD. The dorsal nucleus of the lateral lemniscus in the mustache bat: monaural properties. Hear Res 1993;71:51-63.

31. Irvine DRF. The auditory brainstem. In: Autrum H, Ottoson D, eds. Progress in sensory physiology 7. Berlin, Germany: Springer-Verlag, 1986:212-28.

32. Li L, Kelly JB. Inhibitory influence of the dorsal nucleus of the lateral lemniscus on binaural responses in the rat's inferior colliculus. J Neurosci 1992;12:4530-9.

33. Faingold CL, Boersma-Anderson CA, Randall ME. On the role of the dorsal nucleus of the lateral lemniscus in acoustically-evoked inhibition in the inferior colliculus. Hear Res 1993;69:98-106.

34. Park TJ, Pollak GD. GABA shapes sensitivity to interaural intensity disparities in the mustache bat's inferior colliculus: implications for encoding sound location. J Neurosci 1993;13: 2050-67.

35. Markovitz NS, Pollak GD. Binaural processing in the dorsal nucleus of the lateral lemniscus. Hear Res 1994;73:121-40.

36. Yang L, Pollak GD. The roles of GABAergic and glycinergic inhibition on binaural processing in the dorsal nucleus of the lateral lemniscus of the mustache bat. J Neurophysiol 1994; 71:1999-2013.

37. Yang L, Pollak GD. Binaural inhibition in the dorsal nucleus of the lateral lemniscus of the mustache bat affects responses for multiple sound sources. Auditory Neurosci 1994;1: 1-17.

38. Klug A, Park TJ, Pollak GD. GABA and glycine influence binaural processing in the inferior colliculus of the mustache bat. J Neurophysiol 1995;74:1701-13.

Ann Otol Rhinol Laryngol 106:1997

ERADICATION OF COMMUNICATIVE DISORDERS: PREVENTIVE MEDICINE IN THE 21ST CENTURY

ROBERT J. RUBEN, MD
BRONX, NEW YORK

Profound changes in our society occurring over the past few decades have resulted in a major shift in societal emphasis from labor to communication. The widespread use of personal computers has enhanced the importance of information-communication in daily life. People with communication disorders are at substantial risk of underemployment and lowered quality of life. Advances in medical science and hearing health care have placed us on the threshold of being able to correct, rather than remediate, certain types of hearing loss. The finding that auditory hair cells of submammalian species regenerate has stimulated greatly the field of auditory research. A new lexicon is required to describe this emerging field. Methods exist to protect against hearing loss, repair affected structures prior to their degeneration, promote dedifferentiation-redifferentiation of undamaged structures into sensory cells, and, finally, promote regeneration of new sensory cells from precursor cells. Each of these processes has unique requirements, and all may be required to promote the restoration of hearing following damage or disease.

KEY WORDS — communication, hearing loss, prevention.

Dr Gates, Dr Rubel, Dr Weymuller, friends — it is a privilege to be part of the dedication of the Virginia Merrill Bloedel Hearing Research Center. The creation of this center presages what will become the major health concern of the 21st century — communication. The well-being of society is based on the productivity and integration of its members. Our society is now an information-communication society. The cumulative wealth of society and the economic opportunity of individuals derive from individuals' ability to communicate. Today, the wheelchair-bound person can be highly productive through the use of communication skills via a computer, whereas the high school athletic star who has, however, inadequate communication skills is by and large unemployable and disaffected. Deficits in communication skills are associated with an increase in antisocial and criminal behavior.

During the 19th and 20th centuries, the genius of medicine was directed toward the prevention of malnutrition, infection, cancer, and other maladies that diminished a person's ability to do physical labor — the traditional base of a society's wealth. Today, the strength of a society lies in the ability of its people to communicate. The mandate of medicine is the prevention of communication disorders.

The latter part of the 20th century has produced two great scientific advances in the area of communication disorders: 1) restoration of the inner ear and 2) recognition of the synergy between the quality of the linguistic input for a child and his or her hearing capacity for the attainment of optimal communication skills. These two advances will provide the foundation of preventive medicine for communication disorders of the 21st century.

The discoveries that the elasmobrachs — cartilaginous fish — continue to make hair cells throughout life, and that chicks have the ability to add new hair cells to the damaged lagena revealed the possibility that the *end state* cells of the mammalian inner ear could be restored. Evidence indicated that the inner ear of the mammal did have postpartum mitoses in the sensory cells of the posterior labyrinth and in cells of unknown function within the cochlea. Further studies showed that the in vitro environment of the developing mouse could be manipulated so as to result in an increase in the number of outer hair cells. Then, it was found that the cochlea of the adolescent rat, in vitro, had the capacity to replace hair cells that had been destroyed by an aminoglycoside. There have been and there are currently under way many more inquires into the mechanisms of the anatomic restoration of the inner ear in the mammal, and ultimately, these discoveries will be applied to ameliorate the diseases of the human inner ear.

The current diverse information concerning the restoration of the anatomic integrity of the inner ear indicates that there will be at least four different processes that will be applied to human disease: *protection, repair, dedifferentiation-redifferentiation,* and *regeneration.* Each of these mechanisms will require special molecular knowledge of the dis-

---

From the Departments of Otolaryngology and Pediatrics, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York.
CORRESPONDENCE — Robert J. Ruben, MD, Dept of Otolaryngology, Montefiore Medical Center, Gold Zone, Main Floor, 111 E 210th St, Bronx, NY 10467.

ease processes. Let us look at how these process may be applied to the human context.

To consider protection first: work is presently under way that indicates that a number of substances, eg, antioxidants, can protect the spiral ganglion cells from the effect of cancer chemotherapeutic agents. This work is based on knowledge of how the chemotherapeutic agents kill cells and of how this action may be thwarted. *Protection*, such as this, will play a major role in the prevention of hearing loss and consequent communication disorders in the many instances in which sensorineural hearing loss (SNHL) can be anticipated. Some examples are in the acquired domains, such as ototoxic exposures and sound trauma; the latter is based on current toughening studies. In the genetic area, there are numerous genetically determined forms of progressive SNHL. Understanding these maladies at the molecular level will allow for the application of appropriate substances in the inner ear that would prevent the deleterious action of the rogue gene products. The application of these preventive substances may in some instances be of a short duration, eg, to prevent the effects of hearing loss from a course of an ototoxic agent, or it may occur over an extended period, as in the prevention of hearing loss in a person with autosomal dominant progressive deafness.

Repair is a mechanism that is known to occur in the context of the disease process of the inner ear. It is evidenced by the restoration of function, such as that seen in a temporary threshold shift or in the return of speech discrimination following a fistula repair. There is some information that *repair* may be occurring as part of the observed in vitro phenomenon of the replenishment of mammalian hair cells noted above.

The predominant final common pathway for SNHL deafness is the premature death of the sensory and/or neural cells that transduce and transmit the signal to the brain. Almost all studies that have examined over time the anatomic processes of SNHL have observed premature cell death. Studies that have combined physiological or behavioral function with histopathology demonstrate that when there is diminished or even a complete lack of measurable function, hair cells and their supporting cells remain present. It would seem that in most instances, cell death is slow, and that there is a window of opportunity for cell repair. Whether each disease will need a specific repair mechanism, or whether there will be a common pathway, possibly dependent upon growth factors, is not yet known. Probably, combinations of both strategies will be needed. The person with the onset of SNHL will require prompt diagnosis and then an appropriate repair regimen. This strategy must be applied in the fetal state when appropriate, as well as in the postpartum state. At this point, it appears that the application to the fetus would occur after the cellular elements of the inner ear are formed. It is known from the studies of mammalian histopathology that premature cell death is a common factor in most congenital losses, both acquired (eg, congenital rubella) and genetic (eg, the shaker-1 mouse). Exceptions are cases in which there is either agenesis of the inner ear, or severe malformation of the structure of the inner ear, as seen in the Kriesler mouse. Repair interventions will be episodic or repetitive, depending on the nature and duration of the deleterious environment. Repair may have the greatest applicability of all of the mechanisms, for many patients with acquired SNHL can be identified, and most of these will have damaged sensory cells that, it is anticipated, will be amenable to repair.

Dedifferentiation-redifferentiation is a process well known to the cell biologist. Some studies have shown that many hair cells appear to be replaced in a hearing organ, but there appear to be few or no mitoses to account for these newly appearing hair cells. There is, presumably, a mechanism that allows already-formed cells of the inner ear to dedifferentiate and then to redifferentiate into the required sensory cells. This form of anatomic, and presumed functional, restoration will be useful for patients who receive diagnoses after they have had substantial loss of the sensory elements. This may include those with sudden deafness, such as derives from viral labyrinthitis and Cogan's syndrome, or those with genetic disorders that are either not promptly identified or that are characterized by very rapid destruction of the inner ear. The therapy may be applied as a short course if the noxious agent is no longer present, or may need to be continuously available to the inner ear if the destructive agent remains present, such as a genetic abnormality.

The fourth mechanism is *regeneration* of the sensory elements of the inner ear. Regeneration may be considered a special case of the dedifferentiation-redifferentiation phenomena. In regeneration, a cell will have to modify its usual state to enter a mitotic cycle. One or both of the resulting cells will then differentiate into the needed sensory elements of the inner ear. This process will, it is thought, require the proper growth factors that will enable the cell to divide and then may guide it on its new course to become a sensory cell of the inner ear. This form of therapy will be applied to a range of patients similar to those cared for by dedifferentiation-redifferentiation: either those who have lost their inner ear structures very rapidly or those who have been identified late in the course of progressive disease. The administration of the substance that will allow for regeneration will probably be as noted above: a short course for those patients in whom the destructive agent is no longer present, or a chronic supplement for those in whom there is continued presence of pathologic processes.

The cochlea is an organ that transduces sound, via the hair cells, into biologically meaningful energy that causes the spiral ganglion cells to be activated, and they transmit the information to the central nervous system (CNS). (The efferent system is not considered, and its function will need to be compensated.) A question that remains to be answered is, Once the hair cells are again in place, will the neurites have the capacity to connect the hair cells with the CNS effectively? There are, fortunately, two sets of observations that indicate that this may not be an obstacle. The first is the recent report that certain growth factors can preserve spiral ganglion cells, and in addition cause neuritic outgrowth and neuritic contact with hair cells. The second observation, somewhat more general, concerns the plasticity of the CNS to all forms of neural input in the auditory tract. If a cochlear implant can transmit substantial meaningful information, then it is reasonable to anticipate that a repaired, dedifferentiated-redifferentiated, or regenerated organ of Corti connected to the spiral ganglion cells will also transmit information that can be effectively utilized by the CNS.

Currently, techniques being developed to deliver ameliorative substances to the inner ear include placement of osmotic pumps emptying into the scala, transmission through the semipermeable round window membrane, infection of immortalized fibroblasts with genetically engineered viruses that will produce needed substances, entrapment of these "pumping stations" in semipermeable membranes, and placing them into the scala media. Techniques not yet imagined will probably be developed by the 21st century.

In sum, one of our areas of scientific advance allows for the restoration of form and function — a substantial gain for the alleviation of hearing impairment and the prevention of communication disorders. The second area of advance, the recognition of synergy between the quality, as well as quantity, of the linguistic input and the hearing ability of the child for the attainment of optimal communication skills, will play an even greater role in the alleviation of communication disorders. It should not surprise us that the nature of the acoustic input to the CNS via the inner ear will, within limits, change and mold that CNS.

The influence of the auditory environment is inversely proportional to age: the younger the child, the greater the effect. This also is expected, because there is a developmental neuroanatomic model in which neurites of CNS sensory systems decrease until a "steady state" is reached; this is congruent with the behavioral data. The nature of auditory input, from the 6th month of fetal life to probably the 36th month postnatally, is critical for the development of optimal aural communication skills. Prospective clinical studies have shown that the mild fluctuating conductive hearing losses associated with otitis media, when combined with a deficient language environment in the first 12 to 24 months of life, result in significant language deficiencies. These observations indicate that a communication disorder from a hearing loss is dependent on both the degree of loss and the quality of the child's sensory environment. As today's talks will slightly modify each of our CNSs, so will the constant auditory environment of the infant and the toddler change its CNS, and to a much greater degree. If the infant is so unfortunate as to have both a decrease in the amount of sound — the anatomic defect, be it middle ear effusion or SNHL — and also have a diminution of the quality of the linguistic environment, then that child will have a greater resultant communication disorder than if he or she had only one of the deficits. This prospective study also showed that children in inadequate linguistic environments who did not have otitis media with effusion and hearing loss developed adequate language. This and other work leads me to propose that abnormal and/or "perverted" sensory inputs should be recognized as disease vectors, just as a bullet, a virus, a bacterium, or an aberrant gene is considered a disease vector.

Deficiencies of communication resulting from an inadequate language environment can be prevented by ensuring that the linguistic environment is optimal. On the surface, this may seem an unorthodox and new concept of preventive medicine, yet it has foundation in much earlier work. Let us recall the discovery of Abraham Jacobi, who in the late 19th century demonstrated dramatically the necessity of a "nurturing environment" for the survival of foundling infants. When foundlings were raised in a clean, sanitary, but mechanical environment, 100% of them died, but when foundlings were given to the care and handling of wet nurses, the mortality was reduced to only 30% — consistent with the general infant mortality rate of the period. What is proposed is related to what Jacobi proposed more than 100 years ago. The environment — in this case the *linguistic* environment — must be optimal for the child, especially one with even minimal hearing impairment to develop optimal communication skills. The preventive medicine of the 21st century will need to recognize early those children who are in inadequate linguistic environments and implement the conditions essential to the development of imperative communication skills.

The information-communication society depends upon the communication abilities of its members. Today's science has laid the foundations — anatomic restoration and environmental linguistic determination — for the reduction of communication disorders that are associated with the auditory system. The work of prevention depends on the early detection of hearing losses and the identification of children at risk for impaired linguistic exposure. Since, ultimately, it is in its best interest, society will provide the resources needed to extend our knowledge and to apply the information to our population. The Virginia Merrill Bloedel Hearing Research Center will be a vital force in both of these endeavors: the development of new knowledge and its application to the prevention of communication disorders.

Ann Otol Rhinol Laryngol 106:1997

UNRAVELLING THE GENETICS OF DEAFNESS

KAREN P. STEEL, PHD
NOTTINGHAM, ENGLAND

PHILOMENA MBURU, PHD
LONDON, ENGLAND
ANABEL VARELA, BSC
LONDON, ENGLAND
MARY MAHONY, PHD
NOTTINGHAM, ENGLAND
DAVID HARVEY, PHD
NOTTINGHAM, ENGLAND

FERNANDO GIBSON, PHD
LONDON, ENGLAND
KATHRYN BROWN, PHD
LONDON, ENGLAND
JANE FLEMING, PHD
NOTTINGHAM, ENGLAND
JO CABLE, PHD
NOTTINGHAM, ENGLAND

JAMES WALSH, BSC
LONDON, ENGLAND
TIM SELF, BSC
NOTTINGHAM, ENGLAND
ANGELA PEARCE, BSC
NOTTINGHAM, ENGLAND
STEVE D. M. BROWN, PHD
LONDON, ENGLAND

Hearing-impaired mouse mutants not only are good models for human hereditary deafness, but also are extremely useful for understanding the molecular basis of the cochlear defect. We describe here how we identified the gene responsible for the deafness and vestibular defects in the shaker-1 mouse mutant as a myosin VII gene. Three different mutations, all causing the same phenotype in different lines of mouse, were found, providing good evidence that we had, indeed, found the correct gene. The same gene was subsequently found to be involved in Usher's syndrome type 1B, which features deafness, vestibular dysfunction, and progressive retinitis pigmentosa. The myosin VII gene is expressed in sensory hair cells, but not in supporting cells or neurons. We are investigating the role of myosin VII in hair cell development and function. Analysis of the different mutant stocks suggests it has at least two functions. First, it is involved in the development and maintenance of the stereocilia bundle. Second, it has a role in inner hair cell function. No evidence of retinal degeneration like that in Usher's syndrome has been found in the shaker-1 mutants so far studied. The benefits of understanding the function of the gene for families with Usher's type 1B are discussed. This gene is the first to be identified as causing the most common type of disorder in human hearing impairment, neuroepithelial abnormalities, and suggests a new class of candidate genes for involvement in such defects.

KEY WORDS — genetics, hair cell development, hereditary deafness, mouse mutants, positional cloning, stereocilia, Usher's syndrome.

Hereditary deafness is relatively common in the human population, with around half of the 1 in 1,000 children born with a serious hearing impairment having a genetic cause for the impairment. The hearing impairment is sometimes part of a syndrome, and a number of genes have been identified for syndromal deafness (eg, Waardenburg's syndrome types 1 and 2, X-linked Alport's syndrome), but most cases of childhood deafness are nonsyndromal. Autosomal recessive inheritance is particularly common.

It is difficult to study the genetic or biologic basis of deafness directly in humans, partly because there are known to be a number of genes involved in causing deafness that are clinically indistinguishable. Thus, it is usually not helpful to group together different families with genetic deafness to attempt to localize the gene involved to a particular chromosome, because each family is likely to have a different gene at a different location underlying their hearing impairment. Several large families have been used to localize a handful of genes involved in both dominant and recessive nonsyndromal deafness, but even with a very large family, the number of individuals available for study is relatively small, and large numbers of individuals are needed to localize the gene to a sufficiently small region of a chromosome to permit identification of that gene.

Mice do not have this limitation, as a thousand or more offspring can be generated that are all known to carry the same gene causing deafness, making positional cloning of deafness genes a realistic enterprise. Mice have many advantages compared with humans for investigating the development of the inner ear defect, as well as the underlying structural abnormalities and physiological dysfunction. Furthermore, mouse mutants with impaired cochlear function show many similarities to humans with genetic deafness, suggesting that they are likely to be good models for

---

From the MRC Institute of Hearing Research, Nottingham (Steel, Self, Mahony, Fleming, Pearce, Harvey, Cable), and the Department of Biochemistry and Molecular Genetics, St Mary's Hospital Medical School, London (Mburu, Gibson, Walsh, Varela, K. Brown, S. D. M. Brown), England. Supported by the UK Medical Research Council and Hearing Research Trust. This study was performed in full accordance with UK Animals (Scientific Procedures) Act 1986 and the Home Office Code of Practice for Animal Care and Animal Experimentation.

CORRESPONDENCE — Karen P. Steel, PhD, MRC Institute of Hearing Research, University Park, Nottingham NG7 2RD, England.

human hereditary deafness. We use the mouse to identify genes involved in deafness, because once the mouse gene has been identified, it is a rapid step to find the human homologue and look for mutations in people with genetic deafness.

We have particularly focused on genes involved with neuroepithelial-type inner ear abnormalities, with a primary defect in the organ of Corti, rather than genes associated with primary stria vascularis defects (cochleosaccular defects) or with gross malformations of the inner ear (morphogenetic defects), because neuroepithelial defects are probably the most frequent type of disorder found in human genetic deafness. The first gene we have identified that causes neuroepithelial abnormalities is the myosin VII gene, which is altered in shaker-1 mutants.[1]

Shaker-1 is a recessive mutation located on chromosome 7. Shaker-1 homozygotes show typical neuroepithelial-type inner ear defects, with vestibular abnormalities causing hyperactivity, circling and head-tossing, and progressive hearing impairment leading to early deafness. We generated a large intraspecific backcross of 1,066 mice and analyzed DNA from these mice to construct a genetic map of markers in the vicinity of the shaker-1 gene. In this way, we found one marker, Omp, that was inherited together with shaker-1 in all 1,066 mice, suggesting that it is very close to shaker-1 on chromosome 7. Using the Omp clone as a probe, we isolated a number of yeast artificial chromosome (YAC) clones carrying small regions of mouse chromosome 7 including the Omp marker, and we analyzed these YAC clones to look for genes nearby that might be candidates for the shaker-1 gene.

One gene we identified in this way encoded the unconventional myosin known as myosin VII. So far, we have identified the sequence of only part of the gene, extending over about 2 kilobases of sequence that encodes the head domain of the myosin protein, but we are now extending this sequence into the tail domain of the myosin. We were fortunate in having seven different alleles of shaker-1 to search for mutations, and found three different base-change mutations in the myosin VII gene sequence available in DNA from three of the different mutants. This provided strong evidence that the myosin VII was indeed the gene responsible for the shaker-1 phenotype. Two of these mutations would lead to a proline residue instead of an arginine in the predicted protein product, at different sites in the two different alleles, while the third mutation alters a splice acceptor site, which is predicted to lead to exon skipping and a resulting protein with 10 amino acid residues deleted.

The region of mouse chromosome 7 including shaker-1 is known to be homologous to a stretch of human chromosome 11 (11q13) where a gene for Usher's syndrome type 1B (USH1B) has been mapped. Usher's syndrome type 1 involves severe or profound hearing impairment and vestibular dysfunction, similar to that seen in shaker-1 mutants, and also progressive retinitis pigmentosa detectable from about the age of 5 years in children with USH1B. The similarity in phenotype, together with the localization of the two genes in homologous regions of the chromosomes, suggested that the myosin VII gene might be involved in Usher's syndrome as well as in shaker-1. We collaborated with Christine Petit's group in Paris and Bill Kimberling's group in Omaha to look for mutations in human myosin VII in people with USH1B, and quickly found that there were indeed mutations in the same gene.[2]

Myosin VII is part of a large superfamily of myosin molecules,[3] and although it was known that several myosins are present in sensory hair cells, the distribution of myosin VII in the ear was not known. We therefore used in situ hybridization of sections through perinatal mouse heads to detect the presence of myosin VII transcripts. Myosin VII messenger RNA seems to be confined to the sensory hair cell regions of the cochlea and vestibular neuroepithelia, and is not detectable in other areas, including the cochlear and vestibular neurons.

What does myosin VII do in the sensory hair cells? We have a number of hypotheses that we are investigating, based on what we know about the distribution and function of other unconventional myosins. One fairly well-defined role for a myosin in hair cells is to act as an adaptation motor. This motor is responsible for adjusting the tension on the delicate tip links that link the top of one stereocilium to an adjacent stereocilium, which is believed to be important in keeping the tension on the transduction channel (presumed to be at one end of the tip link) at its optimum for maximum sensitivity to mechanical forces. There is good evidence that this motor is a myosin, and although it has been proposed that myosin 1β is involved,[4,5] we suggest that the possible involvement of myosin VII should be investigated, too.

A second area to examine for myosin VII involvement is the kinocilium of vestibular and perinatal cochlear hair cells. The reason for looking at cilia is that myosins are known to be present in cilia, and cilia defects have been proposed previously as a possible site of abnormality in Usher's syndrome (though not necessarily USH1B). A third possible way that myosin VII might affect hair cell function is by having a role in vesicle transport. Several other unconventional myosins are believed to be involved in transporting subcellular vesicles around cells, and myosin VII might also perform such a function. In particular, it might be involved in synaptic vesicle transport, as this is likely to be a vital function for normal inner hair cell activity. We are presently investigating some of these possibilities, and our observations on the mutants so far suggest that myosin VII may have multiple roles.

Of the seven mutations of shaker-1 available, we have identified three (two missense Arg > Pro mutations and a 3' splice site mutation leading to an in-frame deletion) at different sites affecting the head region of the protein. The original shaker-1 mutation, with a missense mutation, has the least severe effect of the seven mutations. The hair cells look ultrastructurally normal for the first few weeks after birth, and the cochlear microphonics develop normally until about 15 days after birth; these findings suggest that the outer hair cells function normally at first. However, the compound action potentials never develop normally; hence, the inner hair cells may be the earliest cell type to be affected in mice with this allele. The other shaker-1 mutations are all more severe in their effects on the cochlea, and most show no signs of any cochlear responses at any stage of development.

The early development of the stereocilia bundles is abnormal, with aberrant bundle arrangement in most hair cells from birth onward, followed by rapid hair cell degeneration. These findings suggest that myosin VII has at least two functions in the inner ear. First, it is involved with organization of the stereocilia bundles. Second, it has another role in inner hair cell function, because in the original shaker-1 allele, the mutant myosin permits normal stereocilia bundle formation, but affects cochlear responses later in development. In all shaker-1 alleles, the hair cells ultimately degenerate, but whether this suggests a third role for myosin VII, in maintenance of hair cell integrity, or is simply a secondary effect of hair cell dysfunction is not clear.

As mentioned above, we have shown that the human homologue of shaker-1 is the gene affected in USH1B, in which progressive retinitis pigmentosa accompanies the auditory and vestibular defects. We have looked at retinal function by electroretinography, but have seen no evidence of systematic differences in thresholds for responses between mutants and littermate controls up to a year of age. Furthermore, we have examined the retinas of these mutants by transmission electron microscopy, focusing particularly on the cilia that form an integral part of the phototransducer cells, and have seen no evidence of the degeneration that is typical of retinitis pigmentosa. The reason for the difference between mice and humans with myosin VII mutations may be that the retinitis pigmentosa takes a set time to develop, and that we would need to keep mice living far beyond their normal life span to detect the first signs of deterioration of the retina. We are continuing our investigations of retinal function in shaker-1 mutants, because we need to understand what role the myosin VII has in retinal function. This understanding is important, because when we know what the myosin VII does, we can start to think about the possibility of clinical intervention to ameliorate the effects of the mutations on retinal function, and possibly even prevent the onset of retinal degeneration in children known to carry USH1B mutations.

Any future form of intervention will require accurate diagnosis of the affected gene. Even before there is any prospect of treatment, families may wish to take advantage of screening for common USH1B mutations. For example, the family of a young deaf child may wish to know whether the child is likely to develop retinitis pigmentosa later in childhood, as this may help them make decisions about the child's education. For these reasons, we are screening British families with Usher's syndrome to determine the types of mutation that are common in this population, to help establish the feasibility of setting up a screening service.

Positional cloning of genes for deafness in mutant mice is a useful tool not only for establishing the type of gene involved in the particular mutant studied, but also for suggesting the types of gene that could be considered as candidates for other, similar types of deafness. Our finding of a myosin molecule involved in the shaker-1 mutant suggests that genes encoding other myosin molecules, as well as their interacting cytoskeletal proteins, are likely to be good candidates for involvement in other neuroepithelial-type inner ear defects. Furthermore, other mouse mutants with neuroepithelial defects may result from mutations in genes that are directly involved in auditory transduction. We know practically nothing about the molecular basis of auditory transduction, and positional cloning of further genes involved in neuroepithelial defects may prove to be an efficient way of gaining molecular access to the process.

REFERENCES

1. Gibson F, Walsh F, Mburu PO, et al. A type VII myosin encoded by the mouse deafness gene shaker-1. Nature 1995;374: 62-4.
2. Weil D, Blanchard S, Kaplan J, et al. Defective myosin VIIA gene responsible for Usher syndrome type 1B. Nature 1995;374:60-61.

SUPPLEMENT 169 — JULY 1997
Volume 106, Number 7, Part 2

EXTRAESOPHAGEAL PEDIATRIC REFLUX: 24-HOUR DOUBLE-PROBE PH MONITORING IN 222 CHILDREN

JOHN P. LITTLE, MD
BRIAN L. MATTHEWS, MD
MICHAEL S. GLOCK, MD
JAMES A. KOUFMAN, MD
DAVID M. REBOUSSIN, PHD
CHRIS J. LOUGHLIN, MD
WILLIAM F. MCGUIRT, JR, MD

ANNALS
OF OTOLOGY,
RHINOLOGY &
LARYNGOLOGY

Publication of this supplement was supported in part by Medtronic Upper Airway, 8299 Central Ave NE, MSP210, Minneapolis, MN, 55432-2023; and by the Department of Otolaryngology, The Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC 27157-1034.

COPYRIGHT© 1997, ANNALS PUBLISHING COMPANY

EXTRAESOPHAGEAL PEDIATRIC REFLUX: 24-HOUR DOUBLE-PROBE PH MONITORING OF 222 CHILDREN

JOHN P. LITTLE, MD
BRIAN L. MATTHEWS, MD
DAVID M. REBOUSSIN, PHD
MICHAEL S. GLOCK, MD
CHRIS J. LOUGHLIN, MD
JAMES A. KOUFMAN, MD
WILLIAM F. MCGUIRT, JR, MD
WINSTON-SALEM, NORTH CAROLINA

Although extraesophageal gastric reflux has been implicated as a cause of many pediatric airway and respiratory diseases, its prevalence in these conditions remains unknown due to the relative lack of sensitivity and/or specificity of traditional reflux testing methods. A prospective study of 222 children (ages 1 day to 16 years) was performed with 24-hour double-probe (simultaneous esophageal and pharyngeal) pH monitoring. Seventy-six percent (168/222) of the study population had abnormal findings in either one or both of the pH probes. Of those, 46% (78/168) had pharyngeal reflux (extraesophageal gastric acid documented by the pharyngeal probe), despite having normal esophageal acid exposure times according to the esophageal probe. Thus, had the pharyngeal probe not been used, 46% of the children with documented extraesophageal (pharyngeal) reflux would have been falsely presumed to have normal reflux parameters. Patients with laryngeal abnormalities, pulmonary abnormalities, and emesis had significantly more pharyngeal acid reflux ($p < .001$) than patients with nonrespiratory symptoms. These data suggest that extraesophageal reflux may be underestimated by single-probe intraesophageal monitoring alone, and that laryngopharyngeal reflux may play a role in the pathogenesis of the conditions studied.

KEY WORDS — child, esophageal pH monitoring, extraesophageal reflux, gastroesophageal reflux, infant, laryngopharyngeal reflux, neonate, pediatric, pH monitoring, pharyngeal pH monitoring, pharyngeal reflux, reflux.

INTRODUCTION

Gastroesophageal reflux (GER) as a cause of "peptic esophagitis" in adults was first described by Winkelstein in 1935.[1] However, pediatric reflux as a clinical entity was not reported until 1950,[2] and at that time, it was simply considered as one of the causes of vomiting in infants. In the 1970s, Fearon and Brama[3] recognized reflux as a cause of various respiratory symptoms in children. Subsequently, multiple other authors have reported additional respiratory complications of reflux, including recurrent bronchitis, croup, and pneumonia, as well as chronic asthma.[4-7]

During the past decade, reports of "extraesophageal" reflux having effects on the pharynx, larynx, and tracheobronchial tree have appeared more frequently. Reflux has been reported to be associated with, to complicate, or possibly to cause contact ulcer and granuloma,[8,9] laryngomalacia,[10] subglottic stenosis,[11,12] laryngospasm,[13,14] and reflex apnea and bronchoconstriction[14-16] (Table 1[17]). While these reports have suggested an association between reflux and the development of these conditions, it remains difficult to clinically demonstrate the causal role of reflux due to limitations in diagnostic methodology.

Prolonged esophageal pH monitoring was introduced in 1969,[18] but it was not used in an attempt to document extraesophageal reflux until 1986, when

TABLE 1. AIRWAY PROBLEMS ASSOCIATED WITH REFLUX

Aspiration pneumonia
Tracheobronchitis
Tracheal stenosis
Reactive airway disease
Asthma or wheezing
Chronic cough
Hoarseness
Stridor
Subglottic stenosis
Laryngospasm
Choking spells
Obstructive apnea
Central apnea
Acute life-threatening events
Sudden infant death syndrome
Hiccups

Adapted from Herbst and Hilman.[17]

From the Bowman Gray Pediatric Reflux Study Group (all authors) and the Departments of Otolaryngology–Head and Neck Surgery (Little, Matthews, Koufman, Loughlin, McGuirt), Pediatrics-Gastroenterology (Glock), and Public Health Sciences/Biostatistics (Reboussin), Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina.

Presented at the meeting of the American Broncho-Esophagological Association, Orlando, Florida, May 6-7, 1996. Second Place winner of the 1996 Resident Research Award.

CORRESPONDENCE — Brian L. Matthews, MD, Dept of Otolaryngology–Head and Neck Surgery, Bowman Gray School of Medicine, Wake Forest University Medical Center, Medical Center Blvd, Winston-Salem, NC 27157.

TABLE 2. SELECTED DIAGNOSTIC TESTS FOR EXTRAESOPHAGEAL REFLUX

Test	*Sensitivity*	*Specificity*
Double-probe pH monitoring (pharyngeal and esophageal)	Good	Excellent
Single-probe pH monitoring (esophageal only)	Fair	Good
Barium esophagography (cinefluoroscopy)	Poor	Good

TABLE 3. SUBGROUP DISTRIBUTION OF 24-HOUR DOUBLE-PROBE PH STUDIES

Study Group	*n*
Clinical studies	202
Respiratory abnormalities	131
Pulmonary	78
Laryngeal	53
Emesis	47
Nonrespiratory abnormalities	17
Post–Nissen fundoplication	7
Random studies	20

Koufman[19] and Wiener et al[20] demonstrated that pharyngeal reflux could be detected accurately in adults by means of a pH sensor placed in the pharynx behind the laryngeal inlet. Use of this diagnostic method has not been reported previously in a large series of pediatric patients with presumed laryngopharyngeal reflux (LPR).

Laryngopharyngeal reflux is defined as gastric acid reflux to the more proximal level of the pharynx. These reflux episodes pass not only through the lower esophageal sphincter (LES) into the esophagus, but also through the upper esophageal sphincter (UES) into the pharynx, so that supraglottic and glottic laryngeal structures are bathed in refluxate, which may spill over into the subglottic larynx and tracheobronchial tree. While the esophagus is adapted to handle intermittent physiologic reflux,[21] the pharynx, larynx, and tracheobronchial tree are less tolerant of this inflammatory process.[12,19,22,23]

Within the last few years, evidence suggesting that LPR is more common than previously realized has been published. In a series of 1,153 patients, Andze et al[24] reported that approximately 43% of children with reflux have respiratory manifestations as well. Otolaryngologists performing a variety of laryngotracheal procedures have further reported that both adult and pediatric patients with untreated reflux may demonstrate poor healing and restenosis.[11,19,25]

In adult studies, the documentation of LPR, as well as GER, has been shown to be critical in the evaluation of patients with laryngeal and pulmonary symptoms in whom occult reflux is suspected.[19,20,22] Single-probe intraesophageal pH monitoring is relatively insensitive, often leading to the underdiagnosis of reflux disease. This single esophageal probe has failed to detect pharyngeal reflux in a significant number of adult patients, because the recording of the esophageal (lower) probe falls within normal parameters while the pharynx and larynx continue to be bathed in intermittent refluxate.[19] As a result, 24-hour double-probe pH monitoring is currently recognized as the single best means of evaluating GER and LPR in adults.[19,20,26,27]

Because children often cannot relate symptoms that would assist in determining a diagnosis of LPR, reflux testing becomes even more important. Currently, single-probe intraesophageal monitoring is considered the diagnostic test of choice in the evaluation of pediatric reflux disease.[28-31] However, users of this test may mistakenly conclude that the presence or absence of abnormal reflux in the esophagus is consistently predictive of similar findings in the pharynx.

Other tests currently utilized to evaluate GER and LPR include barium esophagography, radionuclide scintigraphy, (modified) Bernstein testing, lipid-laden macrophage sampling, and endoscopy with or without biopsy. All of these tests have advantages and at some time have been held to be the standard for documenting reflux disease. Unfortunately, all of them also have shortcomings, not the least of which are relatively poor sensitivity and/or specificity[19,31-33] (Table 2). Despite these limitations, these tests can be used in a complementary fashion to evaluate pediatric reflux, depending on the individual clinical circumstances.

We report our experience using simultaneous esophageal and pharyngeal pH monitoring in a large series of pediatric patients with presumed LPR. These data suggest that this technique is the best method currently available for the documentation of esophageal and extraesophageal gastric reflux.

MATERIALS AND METHODS

STUDY GROUPS

Over a 2-year period (from November 3, 1993, through November 16, 1995), children predominantly referred from the Pediatric Otolaryngology, Gastroenterology, and Pulmonology services at the Bowman Gray School of Medicine were evaluated by 24-hour double-probe pH monitoring. These patients were divided into subgroups (Table 3) based on their primary diagnosis or symptom:

Group 1: Laryngeal Disorders. Includes hoarse-

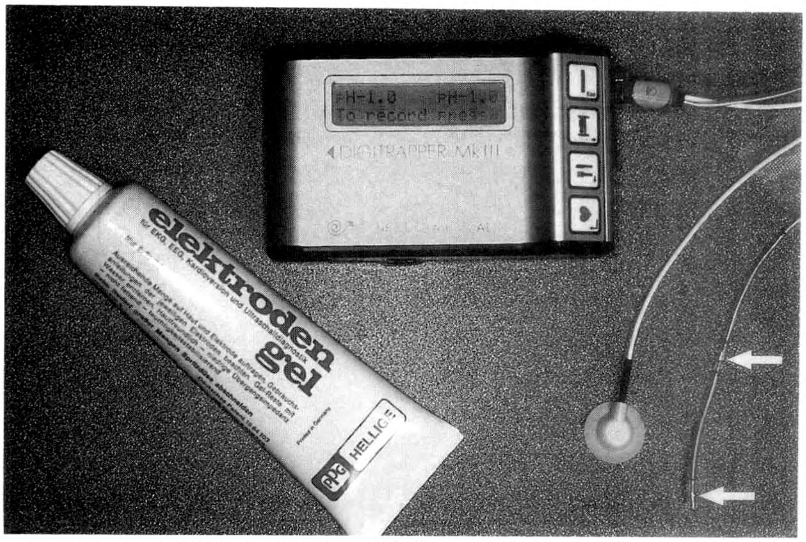


Fig 1. pH probe equipment (left to right): electrode gel, Digitrapper Mark III double-probe pH monitor, skin electrode, and 3-cm double-probe catheter. Arrows — electrodes.

ness, laryngeal edema, laryngeal stenosis, laryngomalacia, laryngospasm, laryngeal papillomatosis, stridor, subglottic stenosis, vocal cord nodules, and vocal cord paresis or paralysis.

Group 2: Pulmonary Disorders. Includes apnea, asthma, chronic cough, recurrent bronchitis or croup, failed extubation, and recurrent pneumonia.

Group 3: Recurrent Emesis. Repeated episodes of vomiting.

Group 4: Nonrespiratory Disorders. Includes bradycardia, cerebral palsy, dyspepsia, dysphagia, esophageal stricture, failure to thrive, poor feeding, back-arching, and other nonrespiratory problems.

Group 5: Post–Nissen Fundoplication. Includes children having previously undergone Nissen fundoplications.

Group 6: Randomly Selected intensive care unit patients. Various disorders, often respiratory (see below).

RANDOMLY SELECTED STUDIES

Random studies were performed on children (Table 3) in the neonatal and pediatric intensive care units with the initial goal of establishing a control group. Three criteria for inclusion in this random series were 1) the child had to have a chest or abdominal radiograph planned or already ordered (to avoid excessive radiation exposure); 2) the child had to be tolerant of the study (as judged by the neonatologist on the basis of overall condition); and 3) reflux testing would not have otherwise been performed. Once the inclusion criteria were met, children were entered into the study pool, from which a random sample was taken. It should be emphasized that these were randomly *selected* children and not normal control patients, due to the fact that they had significant comorbidities (often respiratory disorders) requiring their admission to the respective intensive care units. Despite our interest in accessing a normal, healthy control population, we were unable to secure a true control group.

TECHNIQUE OF PH MONITORING

Equipment. Medtronic Inc, equipment was used for all of the pH studies performed. Two different types of battery-operated monitors were used: the Digitrapper Mark II and the Digitrapper Mark III (model SLP-23000A). The Digitrapper Mark III (Fig 1), used primarily for this study, is considerably smaller (12 × 6.5 × 2.5 cm) than the older Mark II. The Mark III also has a digital clock and an event marker that make it convenient for documenting symptoms during the study period.

The semidisposable silicone rubber catheters (Medtronic Inc, SLC-0200xR where x = interprobe distance in centimeters) utilized for this study (Fig 1) contain two-channel monocrystalline antimony electrodes within a single silicone rubber catheter (a "double probe"). A number of different catheters with fixed pharyngeal-esophageal interprobe distances were used, depending on patient size (3, 5, 7, 10, 12, 15, 18, 20, and 22 cm). The pH catheter diameter (approximately 2.1 mm) is unchanged by the presence of an additional probe. The catheter, therefore, offers no additional disadvantage, other than adjustment for proper positioning, over a single intraesophageal probe. Prior to beginning the study, the probes were calibrated in buffer solutions of pH 1 and pH 7. A reusable silver–silver chloride electrocardiography skin reference electrode (Fig 1) was also positioned adjacent to the catheter.

pH Probe Selection. The double-probe catheters were selected on the basis of the patient's height.

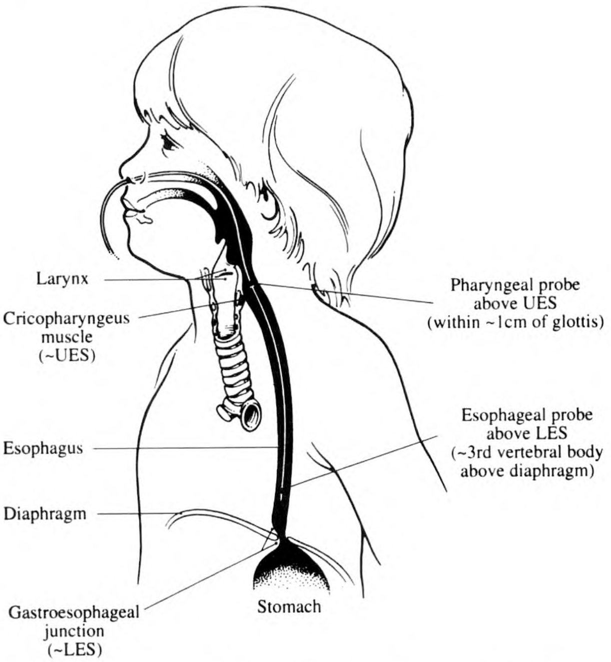

Larynx
Cricopharyngeus muscle (~UES)
Esophagus
Diaphragm
Gastroesophageal junction (~LES)
Stomach
Pharyngeal probe above UES (within ~1cm of glottis)
Esophageal probe above LES (~3rd vertebral body above diaphragm)

Fig 2. Diagram of ideal pH probe placement. UES — upper esophageal sphincter, LES — lower esophageal sphincter.

Previous protocols for single intraesophageal pH probe placement were described by the Working Group of the European Society of Pediatric Gastroenterology and Nutrition (ESPGN).[30] The nasal formula of Strobel et al[34] was used to estimate the position of the LES: [cm length from nares to LES] = [5 + (0.252 × cm height)], with the following modifications: for children less than 5 years old, the lower probe was placed 3 cm above the calculated LES; for children 5 years old or older, the lower probe was placed 5 cm above the calculated LES. Patient age and size aided in determining the interprobe distance to be used in each child. We performed manometry in 3 older children as an adjunctive means of confirming probe placement.

Double Probe Placement. Double-probe pH monitoring was used to evaluate reflux to both the esophageal and pharyngeal levels. The esophageal (lower) probe was placed at approximately the third vertebral body above the diaphragm, according to previously described protocols.[30] The pharyngeal (upper) probe was placed superior to the UES, usually within 1 cm of the laryngeal glottis (Fig 2). It was important to ensure that the upper probe did not reside in the oropharynx, where drying of the electrode can occasionally result in inaccurate measurements ("pseudoreflux episodes").

The pH probe was secured to the cheek with Hytape and/or Tegaderm, with the excess tubing being brought over the ipsilateral ear (Fig 3). A grounding skin electrode was applied and secured to either the child's back or stomach, depending on the child's activity level and positioning.

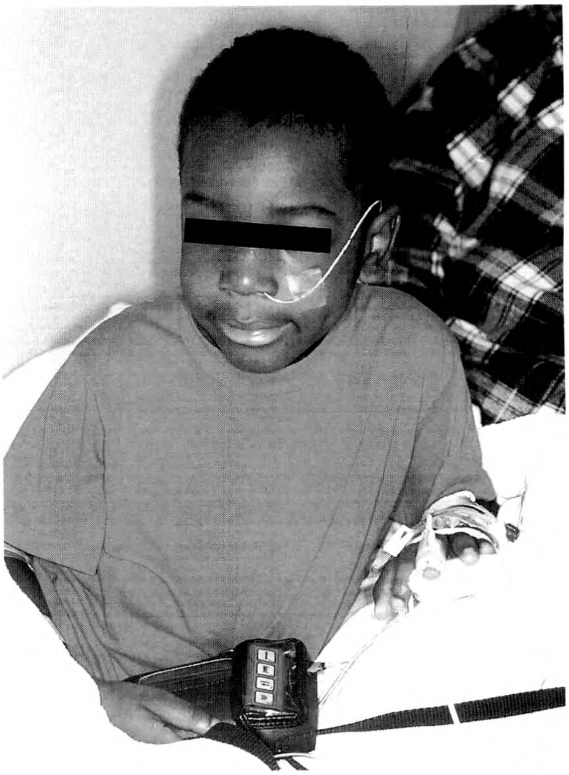


Fig 3. pH probe equipment in child undergoing double-probe pH study.

Verification of Double Probe Positioning. After initial placement of the probe, a lateral chest x-ray (Fig 4) or a portable anteroposterior chest x-ray (for intensive care patients) was obtained to document accurate positioning. The laryngeal ventricle, the epiglottis, and the arytenoid soft tissue prominence were used as landmarks to approximate the level of the laryngeal glottis. The left hemidiaphragm, gastric bubble, and vertebral bodies were used as landmarks for assessment of lower probe placement.

After review of the radiographs, the probes were adjusted when necessary to optimize positioning relative to the approximate UES and LES. Although the pharyngeal (upper) probe was given a higher priority with regard to optimal placement, in almost every case both probes could be properly positioned.

24-Hour pH Monitoring. Once the pH probes were placed and adjusted, monitoring was, ideally, maintained for 24 hours. The majority of the study subjects were admitted for overnight observation during the study, while some were already inpatients receiving other diagnostic testing and treatment. In-patient hospital monitoring allowed for better monitoring and, more important, better documentation on the

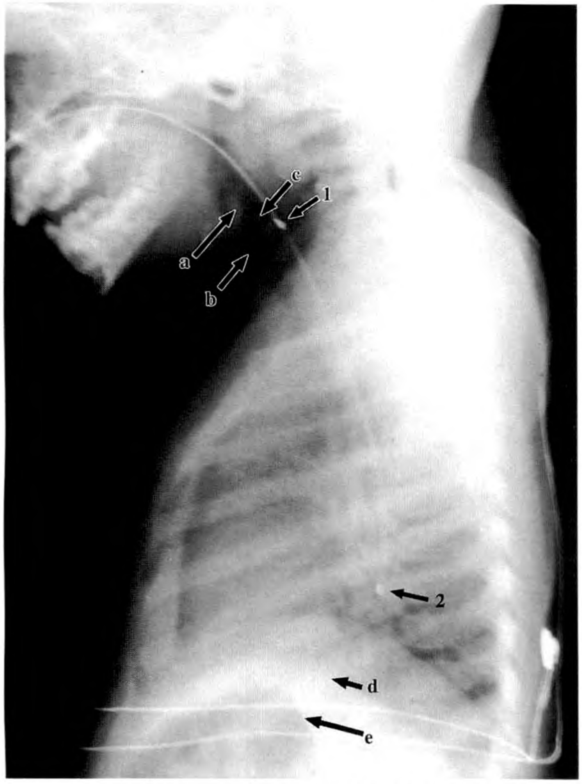


Fig 4. Lateral chest radiograph (with soft tissue penetration). a — epiglottis, b — glottis, c — arytenoid prominence, d — left hemidiaphragm, e — gastric bubble, 1 — pharyngeal probe, 2 — esophageal probe.

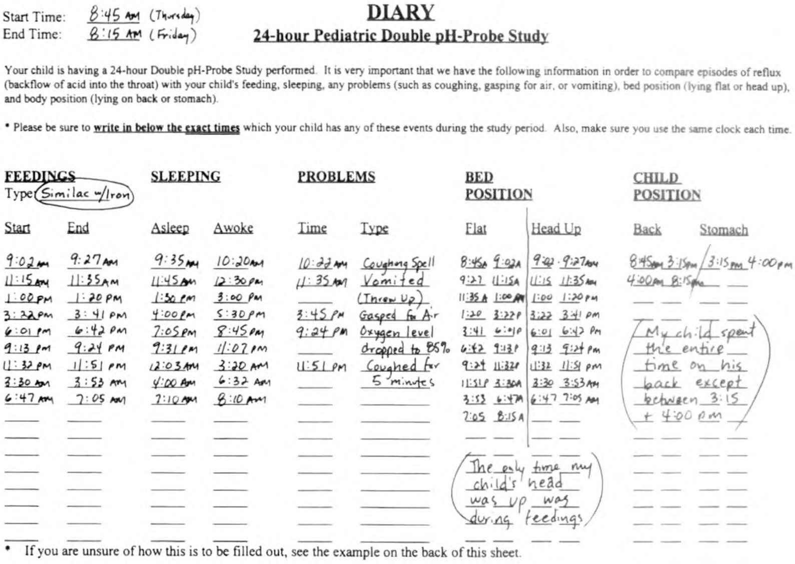
diary sheet of apneic, bradycardic, and oxygen desaturation episodes, as well as other events occurring during the study period. Six older children were allowed to undergo their studies on an outpatient basis.

Study Diary Sheet. A study diary (Fig 5) was maintained for every child. Information recorded included the interval, timing, and type of feeding, the timing of periods of sleep and wakefulness, and the positioning of the child and the bed. Abnormal symptoms and signs, such as coughing paroxysms, oxygen desaturation, respiratory distress, emesis, apnea, and bradycardia, were also recorded on the diary sheet.

Definition of Reflux Episode. A reflux event (Fig 6) was defined as an episode of acid reflux with a pH of ≤4, detected by the probe's electrode, that lasted at least 4 seconds. If another reflux episode occurred within 30 seconds of a previous episode, it was considered to be part of the same episode. The reflux episode ended when the pH level again rose to a level of >4.

The reflux index (RI) was calculated by dividing the total number of reflux episodes by the duration of the study; this provides the number of reflux episodes per hour. (This is slightly different from the RI of Vandenplas and Sacré-Smits,[28] who calculate the RI in the esophagus as the percentage of time the pH level is ≤4.)

Study Completion. Subjects were studied for approximately 24 hours. At the completion of the study, the probe was removed and the monitor was delivered to the pH laboratory, where its stored information was downloaded onto an IBM-compatible personal computer. The EsopHogram software program (SWS-10000), obtained through Medtronic Inc, was then utilized to review the events recorded on the esophageal and pharyngeal probes (Fig 6). Information from the diary sheet(s) regarding feedings, symptomatic events, and positioning was also correlated and entered into this program. As might be expected, there was some variability in the documentation of information on the diary. For the most part, however, parents and nursing staff were quite diligent in recording the requested information, especially with



Start Time: 8:45 AM (Thursday)
End Time: 8:15 AM (Friday)

DIARY

24-hour Pediatric Double pH-Probe Study

Your child is having a 24-hour Double pH-Probe Study performed. It is very important that we have the following information in order to compare episodes of reflux (backflow of acid into the throat) with your child's feeding, sleeping, any problems (such as coughing, gasping for air, or vomiting), bed position (lying flat or head up), and body position (lying on back or stomach).

• Please be sure to **write in below the exact times** which your child has any of these events during the study period. Also, make sure you use the same clock each time.

FEEDINGS
Type (Similac w/Iron)

FEEDINGS		SLEEPING		PROBLEMS		BED POSITION				CHILD POSITION			
Start	End	Asleep	Awoke	Time	Type	Flat		Head Up		Back		Stomach	
9:02 AM	9:27 AM	9:35 AM	10:20 AM	10:22 AM	Coughing Spell	8:45A	9:02A	9:02	9:27 AM	8:45 AM	3:15 PM	3:15 PM	4:00 PM
11:15 AM	11:35 AM	11:45 AM	12:30 PM	11:35 AM	Vomited	9:27	11:15A	11:15	11:35 AM	4:00 PM	8:15 PM		
1:00 PM	1:20 PM	1:30 PM	3:00 PM		(Threw Up)	11:35A	1:00 PM	1:00	1:20 PM				
3:22 PM	3:41 PM	4:00 PM	5:30 PM	3:45 PM	Gasped for Air	1:20	3:22P	3:22	3:41 PM				
6:01 PM	6:42 PM	7:05 PM	8:45 PM	9:24 PM	Oxygen level	3:41	6:01P	6:01	6:42 PM				
9:13 PM	9:24 PM	9:31 PM	11:07 PM		dropped to 85%	6:42	9:13P	9:13	9:24 PM				
11:32 PM	11:51 PM	12:03 AM	3:20 AM	11:51 PM	Coughed for	9:24	11:32P	11:32	11:51 PM				
3:30 AM	3:53 AM	4:00 AM	6:32 AM		5 minutes	11:51P	3:30A	3:30	3:53 AM				
6:47 AM	7:05 AM	7:10 AM	8:10 AM			3:53	6:47A	6:47	7:05 AM				
						7:05	8:15A						

My child spent the entire time on his back except between 3:15 + 4:00 pm

The only time my child's head was up was during feedings

• If you are unsure of how this is to be filled out, see the example on the back of this sheet.

Fig 5. Diary for pH monitoring.

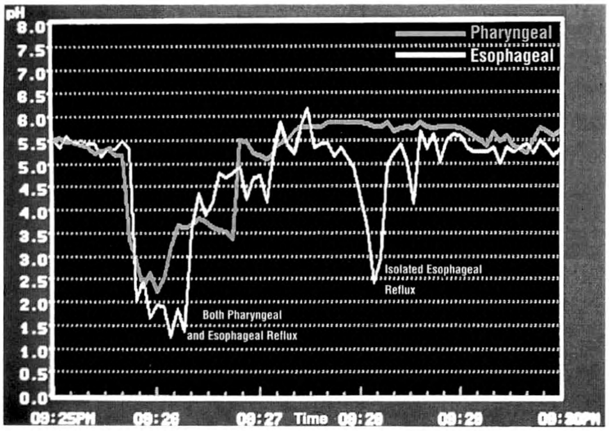


Fig 6. EsopHogram software tracing of two reflux episodes.

regard to feedings and symptoms during the study.

The study yielded the following information for both the upper (pharyngeal) and lower (esophageal) pH probes: duration of study, number of pharyngeal episodes, number of pharyngeal episodes longer than 5 minutes, longest reflux episode, total time pH was ≤4, fraction of time pH was ≤4, RI, and symptom index. A manual review of the computer-generated data was performed to ensure the recording of true reflux events in both probes. In addition, pericibal events (during and within 5 minutes of the documented time of feeding) were factored out of each study, as these often represent the ingestion of acidic liquids and foods.

Normal Values. Normal values for pH monitoring with a single intraesophageal probe vary significantly with patient age and depending on which study one reviews. Vandenplas et al[28,35] have reported their results on single-probe monitoring in 285 and 509 healthy children younger than 16 months screened for sudden infant death syndrome. In their earlier, smaller series, the normal percent esophageal acid exposure time varied with age: 3.02% at 5 to 15 days, 11.37% at 7.5 to 8.5 months, and 6.45% at 14 to 16 months.[28] In their latter series of 509 patients, Vandenplas et al[35] determined that the esophageal RI was the most reliable parameter to evaluate, and provided both a "frequency distribution of RI" table and percentiles for RI. Because the total number of reflux episodes, and not the duration of pharyngeal acid exposure, has been found to more closely correlate with the severity of extraesophageal disease in adults, the pharyngeal RI used in this study was based on the number of pharyngeal reflux episodes in the study period.

Due to the ethical difficulty in obtaining a normal control group and the fact that no previous large series of pharyngeal pH monitoring has been performed, we have no normal values for the pharyngeal probe measurements. Adult studies imply that any acid presence (≥1 reflux episode) in the pharynx is an abnormal event.[11,19] Whether this definition of normal can be appropriately transferred to children is currently impossible to prove. From a theoretic point of view, a single positive pharyngeal reflux event is "proof" of extraesophageal reflux; however, the clinical significance (interpretation) of positive pharyngeal pH events in individual patients remains uncertain at this time. This is because the causal role of extraesophageal reflux in the development of airway diseases cannot be proven by "association data" alone, and because normative pharyngeal reflux data are not available. Some clinicians use symptom correlation as a strong indicator of a positive or "abnormal" study, rather than applying a strict cutoff for normalcy.

In dogs with subglottic mucosal lesions, a single episode of acid and/or pepsin exposure every other day for 3 to 4 weeks has been shown to cause significantly greater inflammation and stenosis as compared to controls.[12] The implications of this finding for children with airway disease, and especially those with airway mucosal lesions, is important. Whether and to what extent pharyngeal reflux in a child is physiologic or pathologic remains to be determined. Determination of the significance of extraesophageal reflux (ie, normal versus abnormal) must take into account each patient's individual disease process and progression. In our experience, if a child has significant airway or respiratory problems along with documented extraesophageal reflux, then the clinician's threshold for antireflux treatment should be lowered.

STATISTICAL METHODS OF ANALYSIS

Four variables were analyzed as dependent measures: 1) pharyngeal RI, 2) esophageal RI, 3) total number of pharyngeal episodes, and 4) total percent esophageal acid exposure time. As noted by previous authors, continuous pH monitoring data are not normally distributed, but rather, skewed.[28] In order to better satisfy modeling assumptions for our comparison of diagnostic groups, we analyzed all dependent variables on a logarithmic scale. More important, this transformation reduces the influence of outlying values.

Differences between diagnostic groups on each dependent measure were assessed by analysis of variance and analysis of covariance models. For each model, a global test of the null hypothesis that no detectable differences exist was made. If this hypothesis was rejected, post hoc *t*-tests comparing sub-

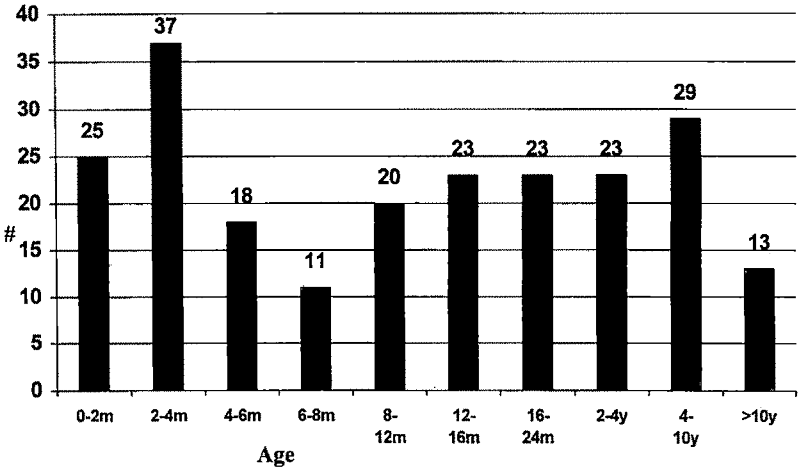


Fig 7. Age ranges of study children.

groups were performed.

RESULTS

Double-probe pH monitoring was completed on 222 of 227 patients over a 2-year period. Five studies from the clinical group were excluded from the data analysis due to improper probe placement. Two hundred two of the studies were "clinical studies" in patients with suspected reflux. Twenty of these patients were randomly selected from the neonatal and pediatric intensive care units, and while they were not suspected of having reflux, it should be emphasized that they were not truly normal controls. Ninety-five female and 127 male patients were studied, ranging in age from 1 day to 16 years old (mean age 27 months; Fig 7). Age and sex were initially included as covariates, but were found not to be significant and were thus eliminated from further analysis. The average time of pH monitoring for all of these studies was 22 hours 23 minutes.

PHARYNGEAL VERSUS ESOPHAGEAL PROBE RESULTS

Seventy-six percent (168/222) of the entire study population had significant acid reflux documented by either the esophageal probe or the pharyngeal probe. Of those, 54% (90/168) had abnormal reflux documented by the esophageal probe, 95% (160/168) had pharyngeal reflux documented by the pharyngeal probe, and 49% (82/168) had significant acid exposure documented by both the esophageal and pharyngeal probes. Forty-six percent (78/168) of these abnormal studies revealed pharyngeal acid reflux despite having normal esophageal acid exposure times. *In other words, had the pharyngeal probe not been in place, 46% of the children with documented pharyngeal reflux would have been presumed to have "normal" reflux parameters.* Even if 2 episodes of pharyngeal reflux in a study period were allowed as "normal," still 30% (50/168) of the children would have been improperly labeled as not having a problem associated with reflux.

SUBGROUP COMPARISONS

The six subgroups shown in Table 4 were evaluated in terms of total pharyngeal episodes, total percent esophageal acid exposure time, pharyngeal RI, esophageal RI, and natural logarithmic transformation of the pharyngeal and esophageal RIs. Mean values for the subgroups are shown in Figs 8 and 9.

The global test for differences among subgroups was significant for all dependent measures (pharyngeal RI, esophageal RI, total number of pharyngeal episodes, and total percent esophageal acid exposure

TABLE 4. OVERALL STATISTICAL ANALYSIS OF SUBGROUPS

Diagnostic Subgroup	*n*	*Mean No. of Pharyngeal Episodes*	*Median No. of Pharyngeal Episodes*	*Mean % Esophageal Acid Exposure Time*	*Median % Esophageal Acid Exposure Time*	*Mean Pharyngeal Reflux Index*	*Mean Esophageal Reflux Index*	*Mean Natural Log Pharyngeal Reflux Index*	*Mean Natural Log Esophageal Reflux Index*
Laryngeal	53	8.19	4.0	7.32	3.70	0.386	3.349	−1.740	0.768
Pulmonary	78	6.05	4.0	5.43	3.60	0.272	3.067	−1.884	0.618
Emesis	47	9.51	5.0	9.73	6.95	0.443	4.320	−1.473	1.105
Nonrespiratory	17	1.82	0.0	4.69	3.00	0.078	2.473	−2.988	0.370
Post-Nissen	7	2.86	0.0	2.19	0.00	0.120	1.313	−2.988	−1.244
Random	20	7.60	0.5	5.11	1.80	0.320	1.841	−2.472	−0.271

Reflux index — number of reflux episodes per hour.

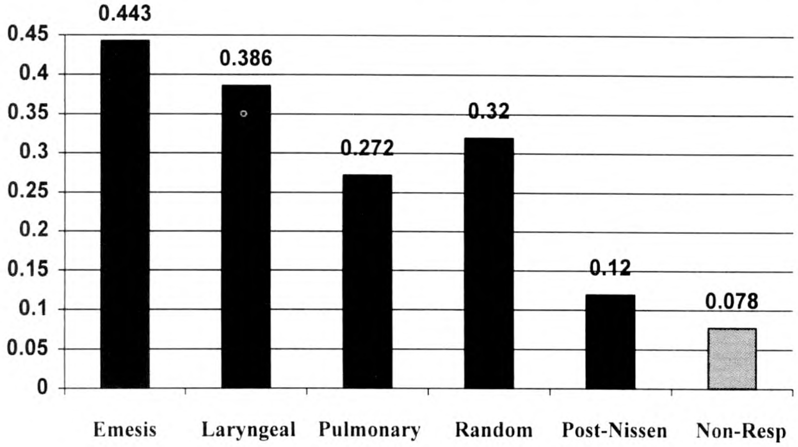


Fig 8. Mean pharyngeal reflux index (number of pharyngeal reflux episodes per hour). Non-Resp — nonrespiratory.

time). Post hoc *t*-tests on all four models showed that the post–Nissen fundoplication group was significantly lower on all measures than the emesis, laryngeal, and pulmonary groups ($p < .05$ for all tests). The nonrespiratory and random groups were significantly lower than the emesis and laryngeal groups on all variables ($p < .05$ for all tests). In addition, no significant differences were found between the laryngeal and pulmonary groups, or between the nonrespiratory and random groups, on any measure ($p > .05$ for all tests). More detailed comparisons of the individual measures are presented below.

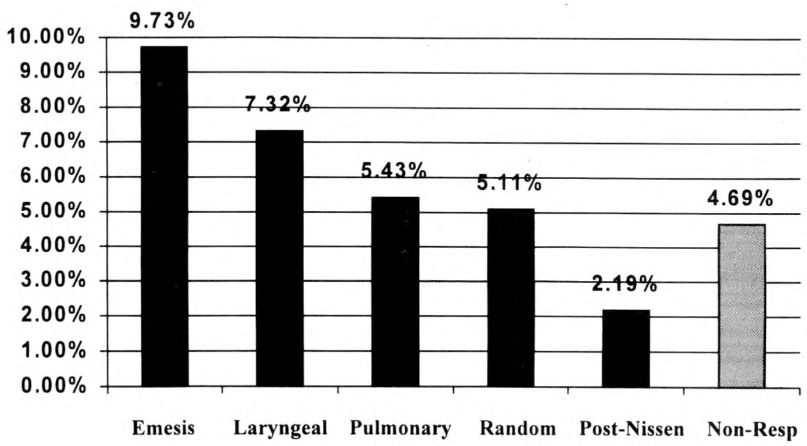
For pharyngeal RI, the emesis, laryngeal, and pulmonary groups were not significantly different from one another ($p > .05$), nor were the random, post-Nissen, and nonrespiratory groups ($p > .05$). Each of the emesis, laryngeal, and pulmonary groups, however, was significantly higher than the random, post-Nissen, and nonrespiratory groups ($p < .05$). The data were consistent with our hypothesis that pharyngeal reflux is associated with the disease processes in the laryngeal, pulmonary, and emesis groups. Results for the total number of pharyngeal episodes were the same, except that the pulmonary and random groups were not significantly different ($p = .061$).

The results for esophageal RI were also consistent with this hypothesis, but the differences were less clear. The emesis and laryngeal groups were significantly higher than the nonrespiratory, random, and post-Nissen groups ($p < .05$), and the pulmonary group was significantly higher than the random and post-Nissen groups ($p < .05$), but the pulmonary and nonrespiratory groups were not significantly different ($p = .233$).

Results for percent esophageal acid exposure time were also consistent with the hypothesis. For this measure, the emesis group was significantly higher than all other groups ($p < .05$), and the post-Nissen group was significantly lower ($p < .05$). The laryngeal and pulmonary groups were significantly higher than the random group ($p = .001$ and $p = .007$, respectively), but were not significantly higher than the nonrespiratory group ($p = .289$ and .111, respectively).

Other Special Categories (Table 5 and Fig 10). The most striking findings of both pharyngeal and esophageal reflux were identified in the laryngomalacia group. Laryngomalacia, in particular, had the highest values for mean and median total pharyngeal episodes, the third highest mean and the highest median percent esophageal acid exposure times, and the highest mean pharyngeal and esophageal RIs (ie, the

Fig 9. Mean percent esophageal acid exposure time.



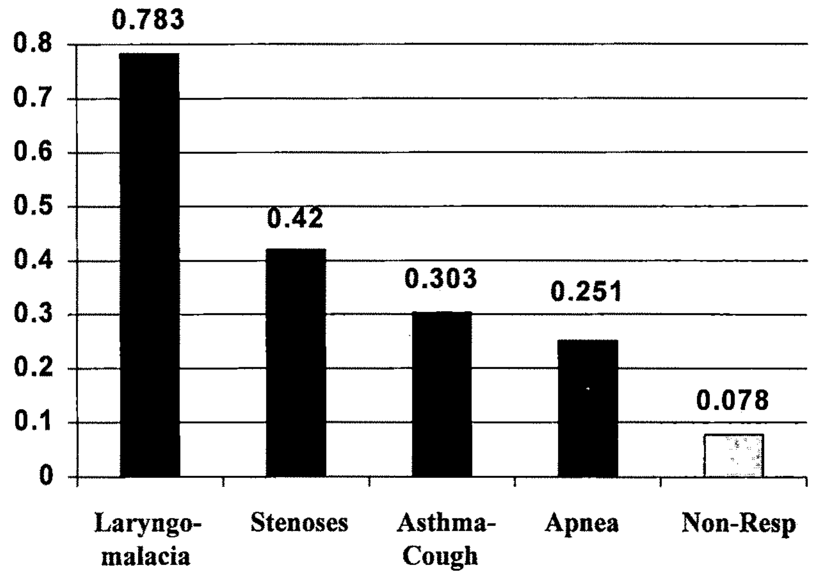


Fig 10. Mean pharyngeal reflux index (number of pharyngeal reflux episodes per hour) for special categories.

highest number of episodes per hour). Other special categories evaluated separately include stenoses (laryngeal and tracheal), asthma or chronic cough, and apnea.

Symptom Correlation. Symptom correlation refers to correlation of abnormal events noted on the diary with reflux episodes. The most notable subgroups for symptom correlation were the pulmonary, emesis, and laryngeal categories. A review of the number of children in each subgroup with symptoms (≥1 episode) that correlated with the number of pharyngeal reflux episodes during the study period revealed the following: pulmonary 36/78 (46%), emesis 34/47 (72%), laryngeal 20/53 (38%), nonrespiratory 7/17 (41%), random 8/20 (40%), and post-Nissen 0/7 (0%).

BARIUM ESOPHAGOGRAPHY

Ninety of the 202 "clinical study" children who completed the 24-hour double-probe pH study underwent barium esophagography with cinefluoroscopy. Of those 90 children, 60% (54/90) had esophageal reflux documented by barium esophagography, and 16% (14/90) had pharyngeal reflux documented by barium esophagography. The results of these radiographic studies were then compared to the results of 24-hour double-probe pH monitoring. The two tests were in agreement with regard to the presence or absence of pharyngeal reflux in 14% (13/90) of the children. Of children with pharyngeal reflux identified by barium esophagography, 21% (3/14) had false-negative results by pH monitoring. In comparison, of the children with pharyngeal reflux identified by pH monitoring, 83% (58/70) had false-negative results by barium esophagography. Our findings support the conclusion that barium esophagography is relatively insensitive in the identification of pharyngeal reflux.[33]

RADIOGRAPHIC REVIEW

A radiographic review was performed on 265 children (222 from this study as well as 43 others) undergoing 24-hour double-probe pH monitoring 1) to assess for adequate double-probe catheter placement (Figs 2 and 4); 2) to identify the appropriate interprobe distance on the double-probe catheters for children of various heights and ages (Table 6); and 3) to identify the ideal probe distance from the nasal inlet for children of various heights and ages (Tables 7 and 8).

Strobel et al[34] have shown that child height is a better measure to use in calculating esophageal length

TABLE 5. SPECIAL CATEGORY ANALYSIS

Special Diagnostic Categories	*n*	*Mean No. of Pharyngeal Episodes*	*Median No. of Pharyngeal Episodes*	*Mean % Esophageal Acid Exposure Time*	*Median % Esophageal Acid Exposure Time*	*Mean Pharyngeal Reflux Index*	*Mean Esophageal Reflux Index*
Laryngomalacia	9	16.89	12	9.41	7.40	0.783	4.646
Stenoses	9	8.67	4	14.12	4.00	0.420	3.986
Asthma or cough	41	6.80	4	6.56	4.80	0.303	3.964
Apnea	22	5.45	2	3.90	3.05	0.251	2.114

Reflux index — number of reflux episodes per hour.

TABLE 6. RECOMMENDED PHARYNGEAL-ESOPHAGEAL INTERPROBE DISTANCE IN CENTIMETERS

Age Range (mo)	*Child Length (cm)*												
	30-40	*40-50*	*50-60*	*60-70*	*70-80*	*80-90*	*90-100*	*100-110*	*110-120*	*120-130*	*130-140*	*140-150*	*>150*
>120									12	15	15	15	
60-120					10		10	12	12	12	15		15
48-60					10		10	12	12	12			
36-48					10	10	10	10					
24-36					10	10	10	10					
21-24				7	10	10	10						
18-21			7	7	10	10							
15-18			7	7	10	10							
12-15			7	7	10								
10-12			7	7	10								
8-10			7	7	7								
6-8		7	7	7	10								
4-6			7	7	7								
3-4	5	7	7	7	10								
2-3		7	7	7									
1-2	5	5	7										
0-1	5	5	7										

than surface area or weight. In their study, Strobel et al used regression methods to identify an equation for esophageal length based on height. This equation was based on measurements in 124 children in whom they performed rapid pull-through esophageal manometry, with 30 of the catheters being brought out through the nose. More recent recommendations from the ESPGN[30] suggest using fluoroscopy to document esophageal probe placement so that the electrode tip lies over the third vertebral body above the diaphragm. This group reported that the formula of Strobel et al was more accurate in children under 12 months of age, but less accurate in older children. Our findings support those of the ESPGN that the Strobel et al formula is often inaccurate. The guidelines recommended (Tables 6-8) in this study are based on the radiographic measurements of 265 children. Data from the radiographic review were entered into linear regression models for predicting interprobe and initial pharyngeal and esophageal placement distances.

Based on our radiographic review, we offer approximate guidelines using child height and age for

TABLE 7. RECOMMENDED PHARYNGEAL (UPPER) PROBE PLACEMENT DISTANCE IN CENTIMETERS FROM NASAL INLET

Age Range (mo)	*Child Length (cm)*												
	30-40	*40-50*	*50-60*	*60-70*	*70-80*	*80-90*	*90-100*	*100-110*	*110-120*	*120-130*	*130-140*	*140-150*	*>150*
>120									16	17	17	18	
60-120					13		14	15	15	15.5	16		18
48-60					12		14	14	15	16			
36-48					12	13	13.5	14					
24-36					12	13	13	14					
21-24				12	12	12.5	13						
18-21			11	11	12	12							
15-18			11	11	12	12							
12-15			11	11	12								
10-12			11	11	12								
8-10			11	11	12								
6-8		10	10	11	12								
4-6			11	11	11.5								
3-4	10	10	10	11	12								
2-3		10	10	11									
1-2	9	10	10										
0-1	9	10	10										

TABLE 8. RECOMMENDED ESOPHAGEAL (LOWER) PROBE PLACEMENT DISTANCE IN CENTIMETERS FROM NASAL INLET

Age Range	*Child Length (cm)*												
(mo)	*30-40*	*40-50*	*50-60*	*60-70*	*70-80*	*80-90*	*90-100*	*100-110*	*110-120*	*120-130*	*130-140*	*140-150*	*>150*
>120									29	31	32	34	
60-120					23		25	27	28	29.5	31		34
48-60					21		25	26	27	29			
36-48					21	23	24.5	25					
24-36					22	22	24	25					
21-24				20	21	22	23						
18-21			18	19.5	21	22							
15-18			19	19.5	21	22							
12-15			19	19	21								
10-12			18	20	21								
8-10			18	19	20.5								
6-8		17	18	19	21								
4-6			18	19	20								
3-4	16	17	17	19	20								
2-3		17	18	18.5									
1-2	15	17	18										
0-1	15	16	17										

1) catheter selection based on interprobe distance and 2) initial placement distance. Catheter selection is critical, as selection of the appropriate interprobe distance helps avoid replacement with another catheter. The use of only one of these probe locations (either pharyngeal or esophageal) is required, since the catheter interprobe distance will determine the position of the other probe. We recommend using the ideal pharyngeal probe location to consistently place this probe above the UES, because, in our experience, the pharyngeal probe site has a smaller margin of error. The reference values provided should allow the majority of double probes to be properly selected and placed. We still encourage the use of a lateral chest radiograph and/or videofluoroscopy with visualization of the neck, chest, and upper abdomen (using soft tissue penetration parameters) to verify placement.

RISKS AND COMPLICATIONS

No major complications were associated with pH probe placement or monitoring in any of the 227 children in this study. A normal gag reflex occurred in many of the children with pharyngeal stimulation during probe placement, with this progressing to an episode of emesis in 2 children. Brief oxygen desaturation was observed in 5 of the children in the neonatal intensive care unit upon initial placement of the probe, although this was a transient occurrence primarily due to general stimulation of the child. The parents were informed of the possibility of these infrequent complications, as well as the potential risks of epistaxis and tracheal intubation with probe placement.

DISCUSSION

Documentation of extraesophageal reflux by pharyngeal pH monitoring does not prove its causal role in the development of the disorders in any of the subgroups studied; however, it does effectively prove the association of LPR with these conditions. While we recognize that the intricate mechanisms of pediatric reflux-induced airway and respiratory diseases remain to be fully elucidated, we believe that our data provide an important first step in defining the role of LPR in the development of these conditions.

Our data indicate that LPR may play an important etiologic role, on the basis of the statistically significant number of pharyngeal reflux episodes occurring in patients with laryngeal and pulmonary diseases as compared with the nonrespiratory group ($p < .001$).

PATHOPHYSIOLOGY OF REFLUX DISEASE

Reflux: Causes and Defense Mechanisms. The major causes of reflux disease[31] include 1) increased frequency of reflux episodes, 2) decreased esophageal clearance of refluxate, 3) increased duration of refluxate exposure, 4) increased noxiousness of refluxate, 5) defective mucosal resistance to refluxate, 6) effects of upper esophageal dysfunction, and 7) the effects of sleep. Four basic lines of defense are described to prevent the adverse effects of gastric reflux: 1) the LES, 2) esophageal acid clearance, 3) esophageal epithelial resistance, and 4) the UES.[19] Because of the smaller caliber of the pediatric airway, an inflammatory process that results in edema and/or impaired healing can be the primary cause or a major complicating factor in the progression of airway

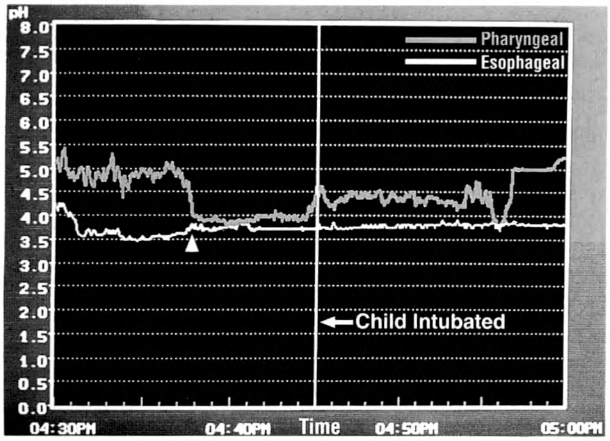


Fig 11. EsopHogram software tracing of episode of respiratory distress requiring intubation, with preceding esophageal and then pharyngeal (arrowhead) reflux.

disease.[7,17]

Esophageal Sphincters. Both the LES and UES are known to be affected by anatomic, neural, hormonal, and chemical factors. The LES has been the focus of the majority of research into GER. It is generally accepted to be a zone of increased intraluminal pressure in the distal 1 to 3 cm of the esophagus, but it is not an easily identified anatomic structure. Many cases of GER are related to anatomic and/or functional abnormalities of the LES.[31]

The UES is overlooked by many in discussions of reflux disease, with most of the attention being given to the LES and other defense mechanisms of the esophagus. Green's[36] review of the UES reveals that it is part of a high-pressure zone present at the junction of the hypopharynx and esophagus. In adults, the high-pressure zone can be as long as 2.5 to 4.5 cm. However, the cricopharyngeus muscle appears to be the only part of the high-pressure zone that has tonic contraction and relaxation patterns typical of a sphincter muscle. The cricopharyngeus muscle in adults is only 1 to 2 cm in length. Radial and longitudinal asymmetry in maximal sphincter pressures has been shown in the anteroposterior and lateral dimensions. The highest anterior pressures in the UES are recorded near the pharynx, while the highest posterior pressures occur closer to the esophagus.[37,38]

Relying on an esophageal pH probe to estimate pharyngeal acid exposure discounts the presence and functioning of the UES. To make a comparison, placing a probe (or probes) in the esophagus to estimate pharyngeal acid exposure is similar to placing a probe in the stomach to estimate esophageal acid exposure.

With reflux to the pharyngeal level, several physiologic factors create a potentially precarious situation for children with airway disorders. Acid clearance mechanisms in the pharynx are not as well developed as those in the esophagus, especially during sleep. In 1988, McConnel,[39] using a solid-state computer to analyze manofluorographic swallowing techniques, reported that peristaltic activity does not occur in the pharynx; rather, the pharynx accomplishes bolus transit by tongue thrust and a secondary suction-pump action of the hypopharynx. The epithelial resistance of the pharynx, larynx, and tracheobronchial tree is also not as well adapted as that of the esophagus to the frequent presence of gastric refluxate.

SPECIFIC AIRWAY AND RESPIRATORY DISEASES

Laryngomalacia. Laryngomalacia involves notable collapse of supraglottic structures, including the epiglottis and aryepiglottic folds, and often results in infantile stridor. It is generally believed to be due to immaturity of the supraglottic cartilaginous superstructure, but the marked association of LPR with this disease makes one reconsider the cause as well as the treatment. Onset can be at birth, but more often, it is first noticed around the first month of life. Endoscopic evaluation will often show associated supraglottic and glottic mucosal edema and/or erythema. Most children with laryngomalacia improve without intervention, but some require medical (eg, corticosteroids, antireflux medication) or surgical (eg, supraglottoplasty, tracheotomy) therapy to prevent recurrent adverse respiratory events. In this study, the children with laryngomalacia had the worst LPR (ie, they had the greatest number of pharyngeal reflux episodes compared to all other subgroups and categories).

Reflux and Respiratory Distress: "Chicken or Egg" Dilemma. Inherent to most respiratory diseases is increased respiratory effort. This increased respiratory difficulty often leads to greater negative intrathoracic pressure, and the possibility of GER or LPR due to this negative intrathoracic pressure. During expiration, increased intra-abdominal pressure tends to compromise LES competence. In addition, lung hyperinflation in asthma lowers the diaphragm and can interfere with the flap valve mechanism produced by the angulated entry of the esophagus into the stomach. Variations in intrathoracic and intra-abdominal pressures have been shown to have a significant effect on one's propensity to reflux.[17,31] A common question that arises in dealing with these patients is whether the respiratory difficulty causes the reflux, or whether the reflux causes the respiratory difficulty. Regardless of causality in this situation, we maintain that the documentation of significant esophageal and pharyngeal acid exposure is an important finding that should be addressed in chil-

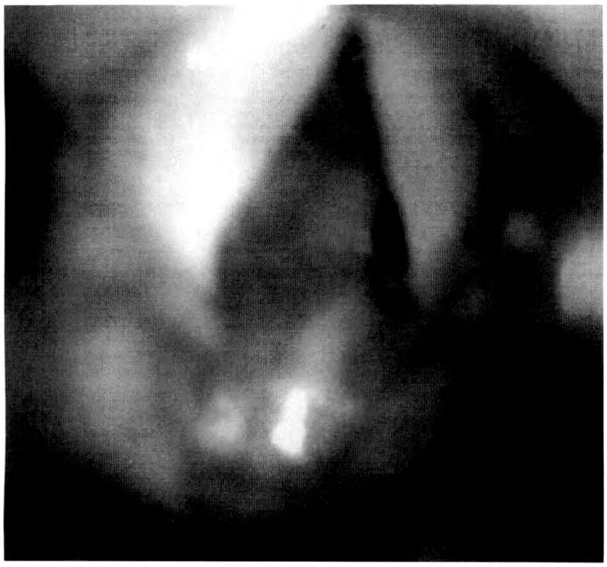


Fig 12. Subglottic stenosis in child with severe reflux disease after prolonged intubation.

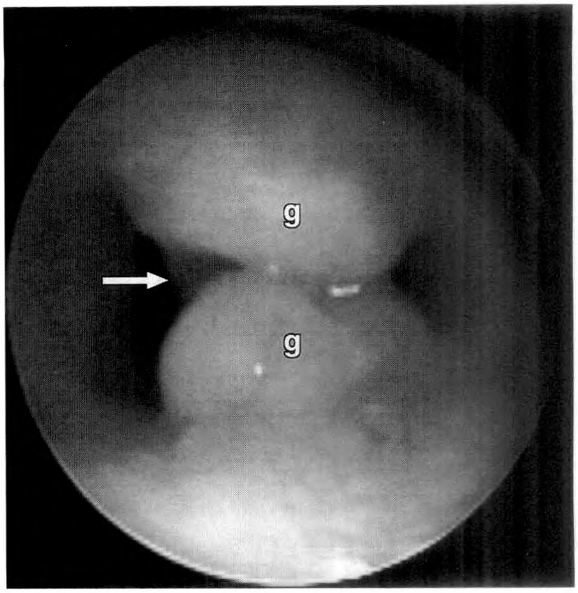


Fig 13. Suprastomal granulation tissue (g). Arrow — tracheostomy tube.

dren with significant respiratory disease.

A specific pH probe study on a child who continued to fail trials of extubation deserves mention as a case that highlights this question of causality. Because of the potential association of reflux with this child's respiratory difficulty, a 24-hour double-probe pH study was performed (Fig 11). This demonstrated at least 15 minutes of esophageal acid exposure (ie, a reflux episode) and approximately 7 minutes of pharyngeal reflux leading to increased respiratory distress and, eventually, reintubation.

Chronic Cough or Asthma. A subset of infants and children with asthma or chronic cough refractory to standard medical therapy has been found to have abnormal GER.[4-7,15,17,24,29,31] Our study supports the association of asthma, chronic cough, and reactive airway disease with LPR. Although pediatricians have long suspected reflux as a causative or exacerbating factor in some children with chronic pulmonary disease,[40,41] adequate documentation of this suspicion has been previously difficult. Single-probe esophageal pH monitoring has allowed for more prolonged evaluation and symptom correlation of disease, and has led to an exponential increase in the number of studies supporting the association of GER with asthma and other chronic pulmonary diseases. Andze et al[24] reported in 1991 that 76% (105) of 139 children with severe asthmatic disease had moderate to severe GER diagnosed by single-probe intraesophageal pH monitoring. Of those, 69% (72/105) had clinical improvement with medical therapy alone, while 88% (29/33) had good to excellent results following surgical therapy. In another study, Berquist et al[42] noted that 49% (40) of 82 patients with recurrent pneumonia and/or clinical asthma had GER verified by two of five tests. Of those patients who underwent medical (12) or surgical (24) therapy for GER, 89% (32/36) had improvement or relief of symptoms.[42] While the extended esophageal pH monitoring, barium esophagography, and radionuclide scintigraphy utilized in these two studies allow an estimation of LPR, none allow consistent documentation. Only a limited number of investigators and clinicians have measured the extent of pharyngeal reflux in children and correlated this to their respiratory disease.[43]

Reflex-Induced Respiratory Disease. While many studies attribute respiratory symptoms to direct exposure of the larynx and tracheobronchial tree to the gastric refluxate, a number of animal studies have documented reflex-induced respiratory symptoms, including bronchoconstriction and apnea, due to the intraesophageal instillation of acid[15] (also Bauman et al, unpublished observations). Chemoreceptors, primarily vagally mediated, are known to exist in both the esophagus and larynx. Two reflex pathways have been demonstrated: the esophagolaryngeal adductor reflex (Sandler et al, unpublished observations) and the laryngeal chemoreflex.[13,44] Whether the respiratory symptoms are due to microaspiration of the refluxate or to reflex-mediated pathways is somewhat controversial, and it is likely that both mechanisms occur to various degrees in different children. Double-probe pH monitoring should provide beneficial information for determining whether GER or LPR is the primary causative mechanism in these children. Isolated GER, without associated LPR, would be a stronger indication of a reflex-mediated respiratory disorder.

Laryngospasm. Recently, Loughlin et al[13] demon-

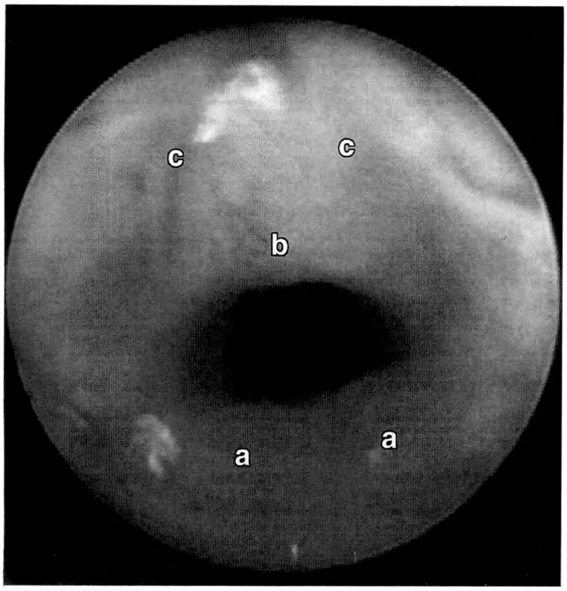


Fig 14. Reflux laryngitis in 12-month-old child. a — arytenoids with posterior commissure edema, b — anterior commissure web, c — false vocal fold edema.

strated a vagally mediated chemoreceptor that consistently induced laryngospasm in canine larynges exposed to a pH solution of 2.5 or less. This chemoreceptor is apparently controlled by the afferent superior laryngeal nerves, since the transection of these nerves abolished the response. Herbst and Hilman[17] suggest that inflammation of the upper esophagus and pharynx due to gastric reflux sensitizes mucosal chemoreceptors, thus further complicating the adverse airway effects of the refluxate. These and other studies continue to raise the question of an association of LPR with sudden infant death syndrome.

Subglottic Stenosis. In a canine model, Little et al[12] demonstrated that applying gastric contents to controlled subglottic mucosal (or cartilaginous) lesions just once every other day for approximately 3 to 4 weeks was sufficient to cause a significant 9-fold increase in the degree of subglottic stenosis in dogs. In that same study, control dogs had saline solution applied to their subglottic lesions, and these dogs only experienced a 1.5-fold increase in stenosis. This study also revealed a significant delay in reepithelialization in the dogs with exposure to gastric contents, and histopathologic evaluation of the dog larynges revealed inflammation, fibroplasia, perichondritis, polypoid degeneration, squamous metaplasia, and submucous gland proliferation. A similar study, performed by Koufman[19] in 1991, revealed that pepsin is the primary injurious agent present in the gastric contents. However, pepsin is biologically active only in the presence of a pH solution of less than 4 to 4.5. Therefore, pH monitoring should reliably measure exposure to acid and activated pepsin.

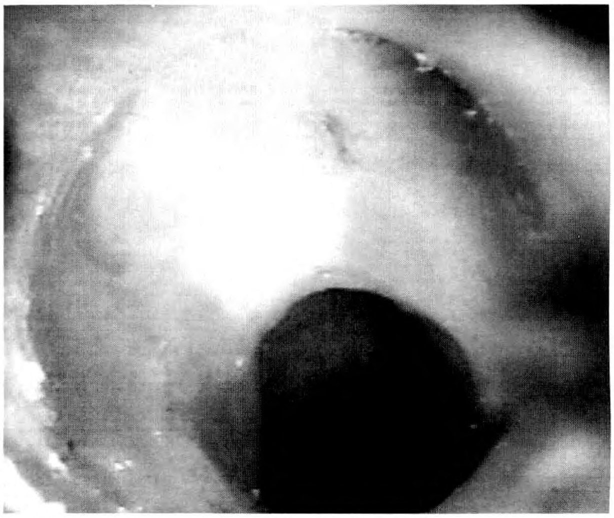


Fig 15. Anterior commissure web in 3-year-old child with laryngeal papillomatosis and associated pharyngeal reflux.

This study is critical to an understanding of the overall pathophysiology of LPR. *It reveals that even infrequent exposure of the laryngotracheal mucosa to the gastric refluxate can have devastating effects on wound healing, and thus, it demands a heightened level of concern on the part of any clinician involved in the care of a patient, especially a child, who has or requires a mucosal lesion in the airway (Figs 12-15).* This study also validates the argument that even one episode of pharyngeal reflux during a 24-hour pH study warrants concern and, most likely, some degree of intervention in a child with airway or respiratory problems.

NORMAL PEDIATRIC CONTROL POPULATIONS?

It has been shown in a limited number of adults and children that any pharyngeal acid exposure is abnormal.[19,45] The UES and normal esophageal peristaltic mechanisms should prevent this occurrence. Physiologic GER is a common event in most, if not all, children. Brief postcibal reflux episodes, occasionally associated with small-volume regurgitation, are frequent occurrences in normal children.

Ethical restrictions prohibit our access to healthy, asymptomatic children, and such access would be required to establish a normal population. However, using single-probe intraesophageal pH monitoring in healthy, asymptomatic children in Belgium in a sudden infant death syndrome screening program, Vandenplas et al[28,35] have determined the normal values for pediatric esophageal acid exposure. These normal values vary with the age of the child, with peak GER measurements occurring around 8 months. At what point the frequency and/or duration of the pharyngeal refluxate becomes pathologic is currently unknown.

An adequate control group for pharyngeal reflux is not easily accessible; therefore, it is not currently possible for studies such as ours to establish normal versus abnormal pharyngeal reflux. What we have identified through this study is that laryngeal abnormalities, pulmonary abnormalities, and emesis have a significant association with pharyngeal reflux. Further, this pharyngeal reflux is more adequately identified by double-probe pharyngeal and esophageal monitoring than by single-probe intraesophageal pH monitoring. In a child with refractory airway problems and documented occult LPR and/or GER, it is incumbent upon the physician to control this exacerbating, or potentially causative, factor.

Questions raised by this study include the following: 1) What is normal pharyngeal acid exposure? 2) Do direct refluxate exposures or reflex mechanisms predominate in reflux-induced respiratory symptoms? 3) Does reflux precede respiratory difficulty, or vice versa? 4) What therapeutic interventions effectively decrease pharyngeal acid exposure?

CONCLUSIONS

1. The incidence of LPR is greatly underestimated by current single-probe intraesophageal monitoring.

2. Double-probe pH monitoring (with pH electrodes in the esophagus *and* pharynx) is the most sensitive and one of the most specific diagnostic tests available for the evaluation of LPR.

3. Control of LPR may be an essential component in the successful diagnosis and management of airway and respiratory diseases in many pediatric patients.

Better understanding, identification, and control of reflux should lead to improved outcomes of medical and surgical interventions, as well as decreased morbidity and mortality, in children with LPR and airway diseases.

ACKNOWLEDGMENTS — The authors thank the following individuals for their assistance in the completion of this project: Denise Criss, PA, Faye Williams, and Lisa Nowak, LPN (pH laboratory technicians); Stacy Slone, MS (biostatistics); Matt McDonald, MSIII, April Preston, MD, Thomas Sumner, MD, Jennifer Johnson, and the Pediatric Radiology technicians (radiographic review); Walter Chwals, MD (pediatric surgery); and David Berry, MD (neonatology).

REFERENCES

1. Winkelstein A. Peptic esophagitis: a new entity. JAMA 1935;104:906-9.

2. Berenberg W, Neuhauser EBD. Cardioesophageal relaxation (chalasia) as a cause of vomiting in infants. Pediatrics 1950;5:414-20.

3. Fearon B, Brama I. Esophageal hiatal hernia in infants and children. Ann Otol Rhinol Laryngol 1981;90:387-91.

4. Euler AR, Byrne WJ, Ament ME, et al. Recurrent pulmonary disease in children: a complication of gastroesophageal reflux. Pediatrics 1979;63:47-51.

5. Malfroot A, Vandenplas Y, Verlinden M, Piepsz A, Dab I. Gastroesophageal reflux and unexplained chronic respiratory disease in infants and children. Pediatr Pulmonol 1987;3:208-13.

6. Hoyoux C, Forget P, Lambrechts L, Geubelle F. Chronic bronchopulmonary disease and gastroesophageal reflux in children. Pediatr Pulmonol 1985;1:149-53.

7. Burton DM, Pransky SM, Katz RM, Kearns DB, Seid AB. Pediatric airway manifestations of gastroesophageal reflux. Ann Otol Rhinol Laryngol 1992;101:742-9.

8. Cherry J, Margulies SI. Contact ulcer of the larynx. Laryngoscope 1968;78:1937-40.

9. Delahunty JE, Cherry J. Experimentally produced vocal cord granulomas. Laryngoscope 1968;78:1941-7.

10. Belmont JR, Grundfast K. Congenital laryngeal stridor (laryngomalacia): etiologic factors and associated disorders. Ann Otol Rhinol Laryngol 1984;93:430-7.

11. Jindal JR, Milbrath MM, Shaker R, Hogan WJ, Toohill RJ. Gastroesophageal reflux disease as a likely cause of "idiopathic" subglottic stenosis. Ann Otol Rhinol Laryngol 1994;103:186-91.

12. Little FB, Koufman JA, Kohut RI, Marshall RB. Effect of gastric acid on the pathogenesis of subglottic stenosis. Ann Otol Rhinol Laryngol 1985;94:516-9.

13. Loughlin CJ, Koufman JA, Averill DB, et al. Acid-induced laryngospasm in a canine model. Laryngoscope 1996;106: 1506-9.

14. Bauman NM, Sandler AD, Schmidt C, Maher JW, Smith RJH. Reflex laryngospasm induced by stimulation of distal esophageal afferents. Laryngoscope 1994;104:209-14.

15. Schan CA, Harding SM, Haile JM, Bradley LA, Richter JE. Gastroesophageal reflux–induced bronchoconstriction. Chest 1994;106:731-6.

16. Boggs DF, Bartlett D. Chemical specificity of a laryngeal apneic reflex in puppies. J Appl Physiol Respir Environ Exerc Physiol 1982;53:455-62.

17. Herbst JJ, Hilman BC. Gastroesophageal reflux disease and respiratory sequelae. In: Hilman BC, ed. Pediatric respiratory disease: diagnosis and treatment. Philadelphia, Pa: WB Saunders, 1993:521-32.

18. Spencer J. Prolonged pH recording in the study of gastrooesophageal reflux. Br J Surg 1969;56:912-4.

19. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope 1991;101(suppl 53).

20. Wiener GJ, Copper JB, Wu WC, Koufman JA, Richter JE, Castell DO. Is hoarseness an atypical manifestation of gastroesophageal reflux (GER)? An ambulatory 24-hour pH study [Abstract]. Gastroenterology 1986;90A:1691.

21. Orlando RC. Esophageal epithelial resistance. J Clin Gastroenterol 1986;8(suppl 1):12-6.

22. Gray SD, Hammond E, Hanson DF. Benign pathologic responses of the larynx. Ann Otol Rhinol Laryngol 1995;104:13-8.

23. Ishii Y, Kobayashi J, Kitamura S. Chemotactic factor generation and cell accumulation in acute lung injury induced by endotracheal acid instillation. Prostaglandins Leukot Essent Fatty Acids 1989;37:65-70.

24. Andze GO, Brandt ML, Dickens SV, Bensoussan AL, Blanchard H. Diagnosis and treatment of gastroesophageal reflux in 500 children with respiratory symptoms: the value of pH monitoring. J Pediatr Surg 1991;26:295-300.

25. Gray S, Miller R, Myer CM III, Cotton RT. Adjunctive measures for successful laryngotracheal reconstruction. Ann Otol Rhinol Laryngol 1987;96:509-13.

26. Richter JE, ed. Ambulatory esophageal pH monitoring: practical approach and clinical applications. Tokyo, Japan: Igaku-Shoin, 1991.

27. Toohill RJ, Mushtag E, Grossman TW, et al. Otolaryngologic manifestations of gastroesophageal reflux. In: Sacristan JJ, Alvarez-Vicent J, Bartual F, et al, eds. Proceedings of the XIV World Congress of Otorhinolaryngology, Head and Neck Surgery, September 10-15, 1989. Berkeley, Calif: Kugler and Ghedini, 1990:3005-9.

28. Vandenplas Y, Sacré-Smits L. Continuous 24-hour esophageal pH monitoring in 285 asymptomatic infants 0-15 months old. J Pediatr Gastroenterol Nutr 1987;6:220-4.

29. Jolley SG, Herbst JJ, Johnson DG, Matlak ME, Boos LS. Esophageal pH monitoring during sleep identifies children with respiratory symptoms from gastroesophageal reflux. Gastroenterology 1981;80:1501-6.

30. Working Group of the European Society of Pediatric Gastroenterology and Nutrition (Vandenplas Y, Belli D, Boige J, et al). A standardized protocol for the methodology of esophageal pH monitoring and interpretation of the data for the diagnosis of gastroesophageal reflux. J Pediatr Gastroenterol Nutr 1992;14: 467-71.

31. Orenstein SR. Gastroesophageal reflux. In: Wyllie R, Hyams JS, eds. Pediatric gastrointestinal disease: pathophysiology, diagnosis, management. Philadelphia, Pa: WB Saunders, 1993:337-69.

32. Jamieson GG, Duranceau A. Gastroesophageal reflux. Philadelphia, Pa: WB Saunders, 1988:281.

33. Leonidas JC. Gastroesophageal reflux in infants: role of the upper gastrointestinal series. Am J Radiol 1984;143:1350-1.

34. Strobel CT, Byrne WJ, Ament ME, Euler AR. Correlation of esophageal lengths in children with height: application to the Tuttle test without prior esophageal manometry. J Pediatr 1979; 94:81-4.

35. Vandenplas Y, Goyvaerts H, Helven R, Sacre L. Gastroesophageal reflux, as measured by 24-hour pH monitoring, in 509 healthy infants screened for risk of sudden infant death syndrome. Pediatrics 1991;88:834-40.

36. Green WER. The upper esophageal sphincter. In: Castell DO, Richter JE, Dalton C, eds. Esophageal motility testing. New York, NY: Elsevier, 1987:183-97.

37. Hunt PS, Connell AM, Smiley TB. The cricopharyngeal sphincter in gastric reflux. Gut 1970;11:303-6.

38. Winans CS. The pharyngoesophageal closure mechanism: a manometric study. Gastroenterology 1972;63:768-77.

39. McConnel FMS. Analysis of pressure generation and bolus transit during pharyngeal swallowing. Laryngoscope 1988; 98:71-8.

40. Kennedy JH. "Silent" gastroesophageal reflux: an important but little known cause of pulmonary complications. Dis Chest 1962;42:42-5.

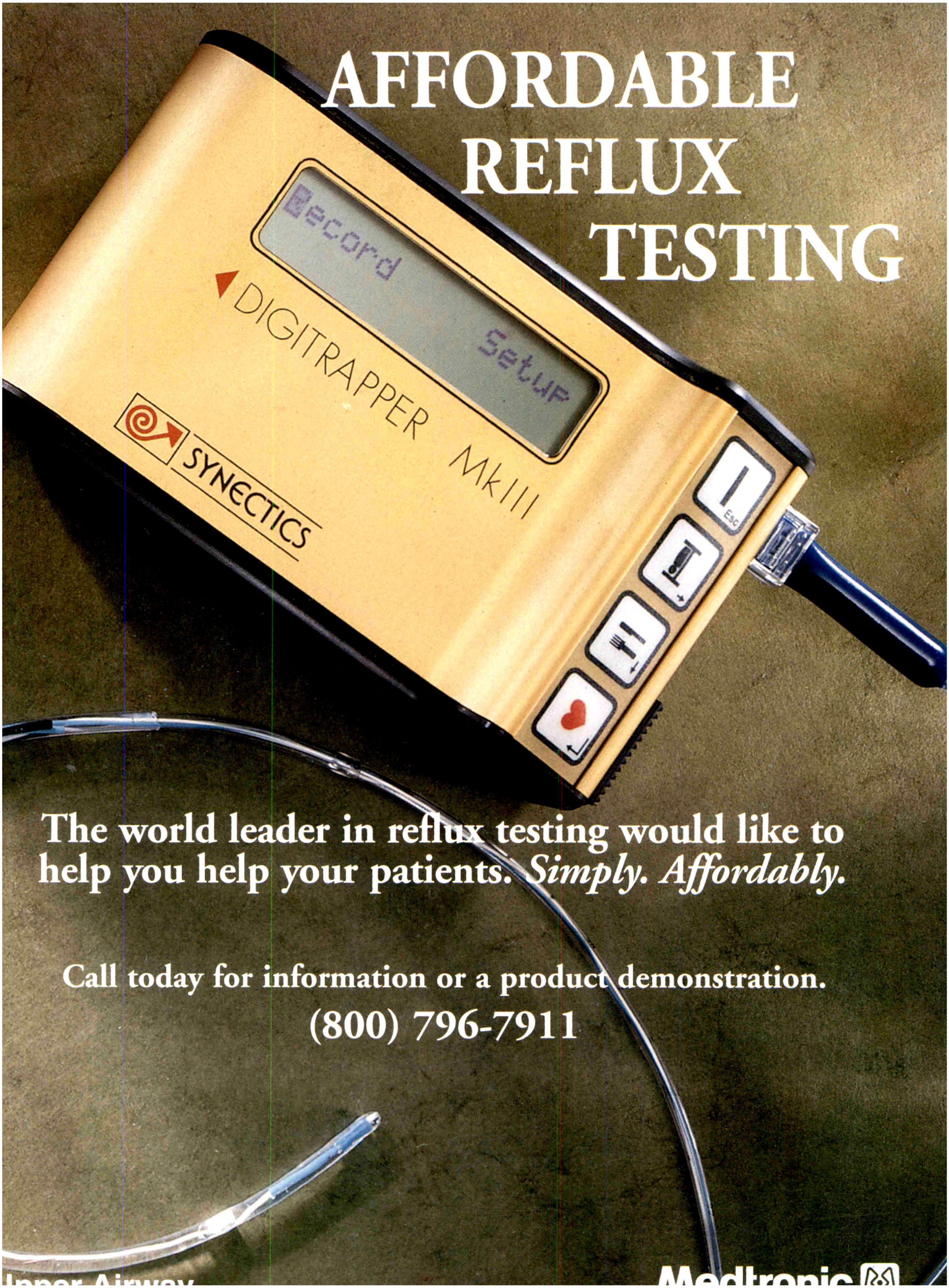
41. Overholt RH, Voorhees RJ. Esophageal reflux as a trigger mechanism in asthma. Dis Chest 1966;49:464-6.

42. Berquist WE, Rachelefsky GS, Kadden M, et al. Gastroesophageal reflux–associated recurrent pneumonia and chronic asthma in children. Pediatrics 1981;68:29-35.

43. Contencin P, Narcy P. Gastropharyngeal reflux in infants and children: a pharyngeal pH monitoring study. Arch Otolaryngol Head Neck Surg 1992;118:1028-30.

44. Lee JC, Stoll B, Downing SE. Properties of the laryngeal chemoreflex in neonatal pigs. Am J Physiol 1977;233:30-7.

45. Haase GM, Ross MN, Gance-Cleveland B, Kolack KE. Extended four-channel esophageal pH monitoring: the importance of acid reflux patterns at the middle and proximal levels. J Pediatr Surg 1988;23:32-7.



AFFORDABLE REFLUX TESTING

The world leader in reflux testing would like to help you help your patients. *Simply. Affordably.*

Call today for information or a product demonstration.
(800) 796-7911

Upper Airway

Medtronic

SUPPLEMENT 170 — SEPTEMBER 1997
Volume 106, Number 9, Part 2

MONTGOMERY® THYROPLASTY IMPLANT SYSTEM

WILLIAM W. MONTGOMERY, MD
STUART K. MONTGOMERY, MBA

ANNALS
OF OTOLOGY,
RHINOLOGY &
LARYNGOLOGY

Publication of this work was supported by
Boston Medical Products, Inc, 117 Flanders Rd, Westborough, MA 01581.

COPYRIGHT© 1997, ANNALS PUBLISHING COMPANY, 4507 LACLEDE AVENUE, ST LOUIS, MO 63108

Ann Otol Rhinol Laryngol 106:1997

MONTGOMERY® THYROPLASTY IMPLANT SYSTEM

WILLIAM W. MONTGOMERY, MD STUART K. MONTGOMERY, MBA
BOSTON, MASSACHUSETTS

A standardized system has been developed to treat unilateral vocal cord paralysis by medialization of the paralyzed cord. The Montgomery® Thyroplasty Implant System consists of a medialization implant, measuring devices, and surgical instruments. The surgical instruments are used to locate, measure, and create a window in the thyroid lamina in which the implant is placed. The measuring devices are used to predetermine the correct implant size. There are five sizes for males (8 to 12 mm) and five for females (6 to 10 mm), with the size representing the distance of medialization. The implant consists of a firm, three-tiered base that locks the implant in the cartilage, and a soft, triangular top that serves to medialize the cord. The standardization of the base allows for revision or reversal at a later date without disturbing the window. The thyroplasty system and surgical procedures are described. Preliminary results of 176 patients who have undergone the Montgomery® Thyroplasty Implant System procedure are presented.

KEY WORDS — laryngoplasty, Montgomery® Thyroplasty Implant System, thyroplasty, unilateral vocal cord paralysis, vocal cord medialization.

Most laryngologists today, when performing a medialization thyroplasty, are carving the implant from a block of silicone at the time of surgery.[1-8] Silicone is difficult to carve, and the edges become rough or irregular. Silicone implants carved at the time of surgery can migrate 1) superiorly, bulging out the ventricular band or supraglottis, 2) inferiorly, bulging out the subglottis, 3) medially, occasionally presenting as a foreign body in the airway, or 4) laterally, negating the effect of the thyroplasty. The hand-carved silicone implant greatly increases the length of surgery. The carved block can also rotate so as to present obliquely in the glottis.

A medialization thyroplasty system has been designed to eliminate the above surgical complications (Boston Medical Products, Inc, Westborough, Mass). The implant presented in this paper is standardized in form and function, thereby eliminating the complications associated with hand-carved silicone implants.

DESIGN OF MONTGOMERY® THYROPLASTY IMPLANT

In this design of the implant, there are two parts (Fig 1A). The lateral, or outer, portion serves to lock the implant to the window made in the thyroid lamina and is constructed from a firm-grade silicone. This lateral portion consists of three rectangular tiers of firm material. The most lateral portion (A on Fig 1B) remains on the outer surface of the thyroid lamina and prevents medial displacement of the implant. The middle portion (B on Fig 1B), which is exactly the same size as the window in the thyroid lamina, stabilizes the implant against any rotation. The inner plate (C on Fig 1B) rests against the inner surface of the thyroid lamina and serves to prevent lateral displacement of the implant. This lateral portion of the implant remains constant for both the male and female larynges. It is firm, yet pliable enough to allow for flexibility during insertion.

The inner, or medial portion (D on Fig 1B) of the implant is used to medialize the vocal cord and the vocal process of the arytenoid. It is triangular in shape and made from a much softer-grade silicone. The hypotenuse of this triangle is designed to correspond to the long axis of the vocal cord when it is in the median position. The base of the triangle is adherent to the inner tier of the outer portion of the implant, which is fixed to the thyroid lamina. Its tip projects posteriorly in order to contact the base of the vocal process of the arytenoid. In so doing, it accomplishes closure of the posterior commissure (Inset, Fig 1B).

The Montgomery® Thyroplasty Implant is radiopaque so that its exact position can be easily demonstrated by radiography postoperatively. The overall contour of the implant is designed so that it will medialize only the true vocal cord and not the ventricle or false cord. There are five sizes for the male larynx and five sizes for the female larynx.

PREOPERATIVE EVALUATION OF PATIENT

The larynx is evaluated by videolaryngoscopy and videolaryngostroboscopy using the Olympus 3 fiber-

---

From the Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

Presented at the meeting of the American Laryngological Association, Scottsdale, Arizona, May 10-11, 1997.

CORRESPONDENCE — William W. Montgomery, MD, Dept of Otolaryngology, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114.

optic scope and a Nagashima rigid scope. The parameters of this evaluation include amplitude, range, fundamental frequency, jitter, and maximum phonation time. This evaluation is repeated 2 months following the medialization thyroplasty operation and again 6 months postoperatively. The purposes of this evaluation are to determine the position of the paralyzed vocal cord (median, paramedian, or lateral), the amount of gap between the vocal cords during phonation, and the function of the opposite, nonparalyzed vocal cord. Photographs are taken during maximum abduction and maximum adduction. These are placed in the patient's record.

ANESTHESIA

A skilled anesthetist or anesthesiologist is essential for the success of this operation. The correct balance between sedation and responsiveness has to be maintained during the entire operation. The suggested anesthesia for thyroplasty in the average 70-kg patient is as follows. Initially, Versed, 1 to 2 mg intravenously, is used in the holding area. Fentanyl citrate, 50 μg/mL, is used in the holding area or on the way to the operating room. In the operating room, fentanyl citrate, 25 μg (×2), is given at the beginning of the operation. Incremental doses of propofol are used 30-20-10 mL, etc.

Prior to use of the fiberoptic laryngoscope, one nasal cavity is sprayed with a mixture of 3% Xylocaine and 2% phenylephrine hydrochloride or packed with a pledget saturated with 4% cocaine hydrochloride solution. The pack remains in place until the introduction of the fiberoptic laryngoscope. The line of the incision and the underlying musculature are injected with 2% Xylocaine and 1:100,000 ephedrine hydrochloride.

Two to 5 minutes prior to insertion of the implant, 50 to 100 mg of lidocaine hydrochloride is administered, followed by additional propofol.

TECHNIQUE OF SURGERY

The patient is prepared and draped as shown in Fig 2. The positions of the thyroid notch, inferior margin of the thyroid lamina, and cricoid cartilages are marked. Hatch marks are scratched along the incision line as shown in Fig 2 to assist with accurate closure. A horizontal incision begins approximately 2 cm from the midline on the contralateral side of the neck at a level just above the inferior border of the thyroid lamina. It extends to the ipsilateral side of the neck just beyond the anterior border of the sternocleidomastoid muscle.

Skin flaps are elevated superiorly and inferiorly in a plane superficial to the fascia covering the strap muscles. The sternohyoid muscles are separated in the midline so as to identify the thyroid notch, the thyroid lamina anteriorly, and the cricothyroid membrane (Fig 3).

The strap muscles on the ipsilateral side of the neck are undermined and retracted laterally so as to expose the thyrohyoid muscle (Fig 4A). If scar tissue exists from previous surgery, it may be necessary to transect these muscles in order to expose the thyrohyoid muscle. Excellent exposure can be accomplished by using two Wheatlander-type self-retaining retractors, or a Wheatlander for vertical exposure and a Gelpi self-retaining retractor for horizontal exposure. Most often, it is not necessary to transect the strap muscles.

The thyrohyoid muscle is transected (Fig 4B) so as to expose the thyroid lamina. The inferior thyroid tubercle is palpated about midway along the inferior border of the thyroid lamina. It is exposed via sharp and blunt dissection.

Surgical instruments have been designed to aid the surgeon in performing the procedure (Fig 5). Included are instruments used to accurately locate and outline the window in the thyroid lamina (Figs 6 and 7). The first instrument, called the Window Caliper, is used to locate the superior border of the thyroplasty window and the anterosuperior corner (key point of the window). There is a caliper designed specifically for male patients, and one specifically for females. After the inferior thyroid tubercle has been exposed and defined, the inferior border of the thyroid lamina is exposed anterior and posterior to this structure. One point of the caliper touches the inferior border of the thyroid lamina, anterior to the thyroid tubercle, and the other, a point directly superior. As the inferior point is lifted free, a Bovie cautery is applied to the tip of the measuring device, and a cautery mark will appear at the superior point (Fig 7A). A similar cautery point is made beginning on the inferior border, posterior to the inferior thyroid tubercle (Fig 7B). Anterior and posterior cautery marks are connected with a marking pen. This line is extended to the anterior aspect of the thyroid lamina (Fig 6A). With the same caliper, a mark is made along this line, beginning at the anterior midline and extending posteriorly. This cautery mark is the point of the anterosuperior corner (key point) of the thyroid lamina window (Figs 6A and 7C). The distance is 7 mm in the female and 9 mm in the male larynx.

OUTLINE OF THYROPLASTY WINDOW

The instrument for making the outline of the window is a specially designed attachment for a standard cautery handle, and is called the Window Outline Instrument (Fig 8A). This instrument is first inserted into the Bovie handle with the tip placed so that the anterosuperior corner and superior border correspond to the key point mark and line on the thyroid lamina (Fig 8B). Current is applied and four marks appear on the cartilage surface (Fig 8C). These marks are connected with a marking pen to complete the outline of the window.

METHOD FOR CUTTING WINDOW

A small tangential electric saw and blade (Fig 9) have been specially designed for the thyroplasty type I operation and other laryngeal framework surgery. The outer perichondrium is not disturbed. This saw can be used in all cases regardless of whether the cartilage has undergone ossification. Cutting the window (Fig 10A) is accomplished with great care so as not to injure the underlying soft tissue. It is best to make the posterior cut first, for occasionally there is troublesome bleeding. Once the four sides of the rectangular window have been cut and the cartilage moves freely, it is grasped anteriorly with the Sharp Hook (small or large) and is carefully separated from the underlying perichondrium with the Chisel Elevator specially designed for this purpose (Fig 10B,C). The rectangular piece of cartilage is removed.

The Window Outline Instrument is then inserted into the thyroplasty window to confirm that the correct-size window has been created (Fig 11A,B). If not, the window can be altered with the thyroplasty saw. A tight fit of the Window Outline Instrument into the window is ideal.

INCISION OF INNER PERICHONDRIUM

Following removal of the cartilage from the window, the inner perichondrium is elevated from the underlying cartilage in all directions (Fig 11C). It is important to elevate the perichondrium posteriorly to the level of the vocal process of the arytenoid. A midline anteroposterior line is cauterized with bipolar cautery or unilateral cautery on a low setting, as indicated in Fig 11D. This line in the inner perichondrium is carefully incised so as to expose the underlying fascia covering the intrinsic laryngeal musculature. This incision is accomplished with a No. 15 surgical blade or delicate scissors. It is our impression that medialization is not as precise when the inner perichondrium is not incised. If the inner perichondrium remains intact, it is tented in by the implant, and undesired medialization occurs inferiorly and superiorly.

MEASURING FOR IMPLANT

At this point, the patient's anesthesia is deepened and one side of the nose is sprayed with 3% Xylocaine with 1% phenylephrine hydrochloride solution, and a fiberoptic laryngoscope is inserted so as to view the larynx (Fig 12A).

A Measuring Device (Fig 12B) is inserted through the window in the thyroid lamina. There are five sizes for both the male and female larynges. When inserted, the Measuring Device accurately simulates the corresponding implant. The vocal cords are observed with a fiberoptic laryngoscope as the Measuring Device is inserted. The end point is complete closure of the vocal chink from the anterior commissure to the posterior commissure and a good voice when the patient is asked to vocalize. The ideal measurement is noted and the corresponding implant is selected (Fig 12C). The size of the implant is noted in the patient's record at this time.

INSERTION OF IMPLANT

Additional anesthesia is given at the time of implant insertion. The Thyroplasty Implant is grasped with broad forceps (Fig 13A), and the posterior tip of the medial triangular portion of the implant is inserted through the window. The posterior slot in the tiered base of the implant is engaged in the posterior rim of the window in the thyroid lamina. A specially designed spatula, the Implant Inserter, is inserted into the slot anteriorly, as a finger applies pressure against the posterior aspect of the implant as shown in Fig 13B. The Thyroplasty Implant is snapped into place with the Implant Inserter (Fig 13C). The three-tiered base locks the implant securely in the window. The size of the implant is visible and should be noted in the patient's record at this time (Fig 13D). If the implant requires change at the time of surgery or change or removal at a later date as a secondary procedure, the anterior end of the external portion of the implant (lateral tier) is grasped with forceps or a hemostat. With lateral pull, the implant snaps out as easily as it was inserted.

REPAIR

The sternohyoid muscles are reapproximated in the midline (Fig 14A) with 3-0 or 4-0 chromic catgut. The platysma and subcutaneous layers are reapproximated with 4-0 chromic catgut, and the skin is repaired with a running suture of 6-0 mild chromic catgut (Fig 14B,C). Butterfly-closed suction drainage is used along with red-top vacuum tubes. To place a butterfly drain, one passes a mosquito hemostat over the sternocleidomastoid muscle to a point 1.5 cm lateral and inferior to the lateral aspect of the

TABLE 1. CAUSES OF UNILATERAL VOCAL CORD PARALYSIS

Cause	*No. of Cases*
Lung (surgery, tumors, aneurysm, heart transplant)	38
Base of skull tumor surgery	30
Thyroidectomy	22
Idiopathic	19
Neck tumor surgery	13
Viral	8
Intubation injury	7
Stroke	7
Carotid endarterectomy	6
Cancer of esophagus	6
Cancer of larynx (cordectomy)	5
Cervical laminectomy	5
Recurrent laryngeal nerve section for spastic dysphonia	2
External laryngeal injury	2
Brain tumor surgery	1
Laryngeal tumor (chondrosarcoma)	1
Resection of hypopharyngeal diverticulum	1
Cricopharyngeal myotomy	1
Cancer of nasopharynx	1
Malignant external otitis	1
Total	176

incision. The skin is tented out, and with a No. 15 blade, one slightly opens the hemostat and makes a small incision over the tip of the hemostat. The tip is then pushed through the skin opening and grasps the end of the butterfly drainage tubing. The drainage tubing is secured in place with a 4-0 silk suture. Steri-strips are applied over the entire suture line after applying Mastosol liquid adhesive or tincture of benzoin to the skin (Fig 14C).

POSTOPERATIVE CARE

1. Medication for pain may be needed the first day. The patient is advised not to whisper or shout. Ordinary conversational voice is permitted.

2. Antibiotics, which were started preoperatively, are continued for 1 week. Intravenous Decadron (8 to 12 mg) is given at the beginning of the operation and continued for 2 additional doses at 8-hour intervals.

3. Red-top vacuum tubes are changed at 2- to 4-hour intervals or as soon as they are one-fourth filled with blood. This requires careful nursing surveillance.

4. The butterfly-closed suction drainage tubing is removed the morning following surgery, and the patient is discharged from the hospital. Same-day discharge is not advised, because of the possibility of laryngeal edema or intralaryngeal bleeding that could interfere with the laryngeal airway.

TABLE 2. SITE OR CAUSE OF NEURAL INJURY

Site or Cause	*No. of Cases*
Recurrent laryngeal nerve in neck	39
Recurrent laryngeal nerve in chest	44
Vagus nerve low in neck	12
Vagus nerve high in neck	18
Base of skull	26
Intracranial	9
Idiopathic	23
After laryngectomy	5
Total	176

5. The implant is radiopaque; thus, if indicated, the exact position of the implant can be easily determined with a computed tomographic scan at the level of the vocal cords by a few 2-mm cuts, along with coronal reconstruction.

6. It is our opinion that evaluation of the patient by videofibrolaryngoscopy or videolaryngostroboscopy and voice analysis is of little value during the immediate postoperative period. The patient is evaluated in 2 months and again at 6 months and 1 year.

EVALUATION OF 176 CONSECUTIVE MEDIALIZATION THYROPLASTIES USING MONTGOMERY® IMPLANT

One hundred seventy-six consecutive cases of unilateral vocal cord paralysis treated with a Montgomery® Thyroplasty Implant are presented. The duration of the implantation ranges from 7 months to 6 years 7 months.

The status of voice, aspiration, and effective cough is based on the patients' subjective assessment and the surgeon's objective assessment. The voice is characterized as normal, slight hoarseness, moderate hoarseness, severe hoarseness, or aphonia. Aspiration is characterized as none, slight, moderate, or complete. Effective cough is divided into normal, moderately effective cough, or no effective cough.

The causes of the unilateral vocal cord paralysis in this series are tabulated in Table 1. The results of the medialization thyroplasty using the Montgomery® Thyroplasty Implant according to the site of the neural injury are analyzed in Tables 2 and 3.

There is not a great difference when comparing the neural sites of the recurrent laryngeal nerves in the neck and chest. The sum of these two sites (83) makes up a good share of the total and demonstrates, on the whole, very good results in improving the voice, controlling aspiration, and providing an ef-

TABLE 3. ANALYSIS OF 176 PATIENTS

	No. of Patients	*Voice*	*Aspiration*	*Effective Cough*
Recurrent nerve (neck, chest, idiopathic)	106	89.6%	99%	99%
Low vagus	12	75%	83%	83%
High vagus	18	83%	72%	72%
Base of skull	26	80.7%	57%	69%
Intracranial	9	66%	77%	77%
Post-hemilaryngectomy	5*			

Data are percentages of patients with improvement after implantation.

*One had no improvement; 2 fair; 2 good.

fective cough. There is very little difference when comparing low and high vagus lesions. The results following surgery for vagal lesions are not as good as those for recurrent laryngeal nerve lesions. Results are even worse when treating base of skull and intracranial lesions. On the other hand, this surgery is well worth the effort in the rehabilitation of these patients. In some of them, simultaneous inferior constrictor myotomy was indicated by modified barium swallow fluoroscopy.

The implant was used in 5 cases of hemilaryngectomy as treatment for cancer of the larynx. All 5 also had a full course of radiotherapy. Sufficient cartilage remained so that a thyroplasty could be performed. Four patients were very satisfied with the improvement in their voices. Aspiration and cough effectiveness were also improved.

In conclusion, it can be said that a medialization thyroplasty using the Montgomery® Thyroplasty Implant is useful in improving the voice quality, decreasing aspiration, and creating effective cough in unilateral laryngeal paralysis. Results are not as good as the neural defect progresses centrally, but on the other hand, the possibility of improvement is well worth the effort.

This is not a true scientific evaluation of the vocal function. We had no voice laboratory during the first 2 years of using this implant. The implant design has gradually improved, and the final design has proven satisfactory. Measuring Devices have been designed to test the degree of medialization of the paralyzed vocal cord necessary to effect a good voice (closure of the glottis) during surgery. These are used to determine the correct size for the implant. A more scientific evaluation of the preoperative, short-term postoperative, and long-term postoperative voice quality will be forthcoming.

In the 176 cases, there were no reactions to the silicone implant. No implants have been displaced medially or laterally, or rotated out of position.

Two cases of laryngeal edema occurred during the immediate postoperative period, requiring an extra day in the hospital for intravenous steroid therapy. In both of these cases, the edema lasted only 3 days. There has been no incidence of tracheotomy.

Five cases required a change in the size of the implant. In 4 cases, it was necessary to increase the size of the implant in order to improve vocal function. The fifth required a reduction in the size of the implant to improve the airway. The incidence of size miscalculation has been significantly reduced with improved instruments and Measuring Devices.

ADVANTAGES OF MONTGOMERY® THYROPLASTY IMPLANT

1. The operation can be performed in much less time than is required for conventional thyroplasty. This is important today, with the rising costs of operating time.

2. By using a Measuring Device, the correct size can be easily determined intraoperatively by visualizing the larynx with a fiberoptic laryngoscope and listening to the patient's phonatory function.

3. The implant is easily inserted and removed. It snaps into place, and no sutures are necessary.

4. Once the implant is inserted, the chance for medial-lateral or superior-inferior displacement or rotation is eliminated.

5. If indicated, the implant can be easily removed without damage to either the cartilaginous or soft tissue structures.

6. Because of the uniformity of the base design, different-size implants can be inserted with no change in the thyroid lamina window.

7. The design of the implant closes the posterior commissure, giving a higher percentage of good postoperative results.

8. The implant is standardized; this eliminates the need to either fashion or alter the implant at the time of surgery. There are five sizes for the male larynx and five sizes for the female larynx.

REFERENCES

1. Isshiki, N, Taira T, Kojima H, Shoji K. Recent modifications in thyroplasty type I. Ann Otol Rhinol Laryngol 1989; 98:777-9.

2. Isshiki N, Tanabe M, Ohkawa M, Kita M. Laryngeal framework surgery for voice disorders. Auris Nasus Larynx 1985;12(suppl 2):217-20.

3. Isshiki N. Recent advances in phonosurgery. Folia Phoniatr (Basel) 1980;32:119-54.

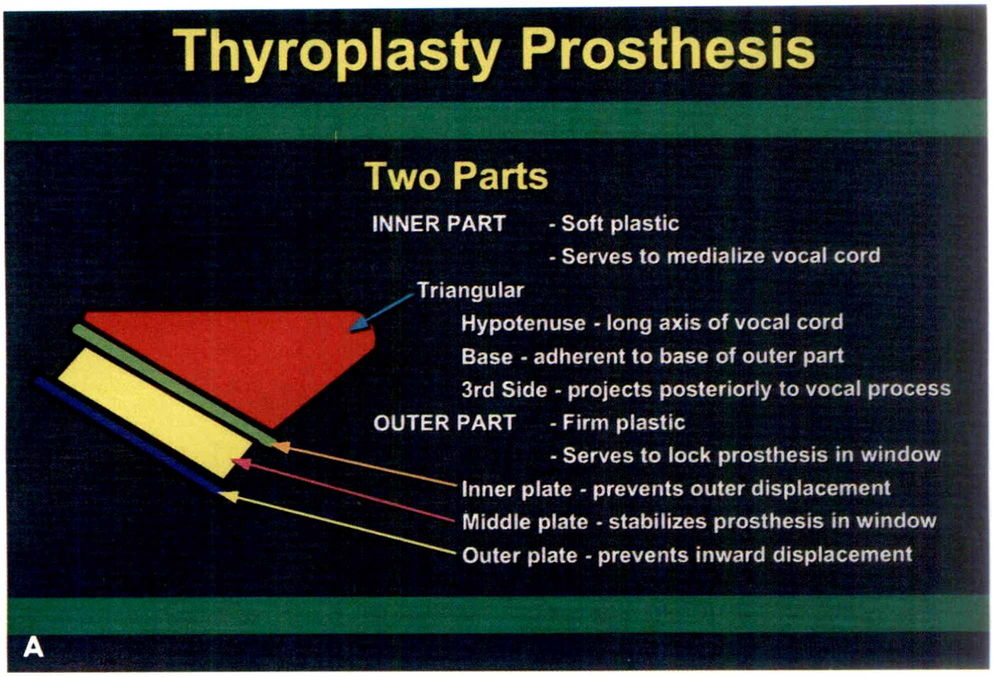
4. Isshiki N, Okamura H, Ishikawa T. Thyroplasty type I (lateral compression) for dysphonia due to vocal cord paralysis or atrophy. Acta Otolaryngol (Stockh) 1975;80:465-73.

5. Isshiki N, Morita H, Okamura H, Hiramoto M. Thyroplasty as a new phonosurgical technique. Acta Otolaryngol (Stockh) 1974;78:451-7.

6. Blaugrund SM, Taira T, El-Assuooty A, Lin P-T, Isshiki N, Gould WJ. Effects of lateral manual compression upon glottic incompetence: objective evaluations. Ann Otol Rhinol Laryngol 1990;99:249-55.

7. Blaugrund SM. Laryngeal framework surgery. In: Ford CN, Bless DM, eds. Phonosurgery. New York, NY: Raven Press, 1991:183-99.

8. Montgomery WW, Blaugrund SM, Varvares MA. Thyroplasty: a new approach. Ann Otol Rhinol Laryngol 1993;102:571-9.



Thyroplasty Prosthesis

Two Parts

INNER PART - Soft plastic
- Serves to medialize vocal cord

Triangular
Hypotenuse - long axis of vocal cord
Base - adherent to base of outer part
3rd Side - projects posteriorly to vocal process

OUTER PART - Firm plastic
- Serves to lock prosthesis in window

Inner plate - prevents outer displacement
Middle plate - stabilizes prosthesis in window
Outer plate - prevents inward displacement

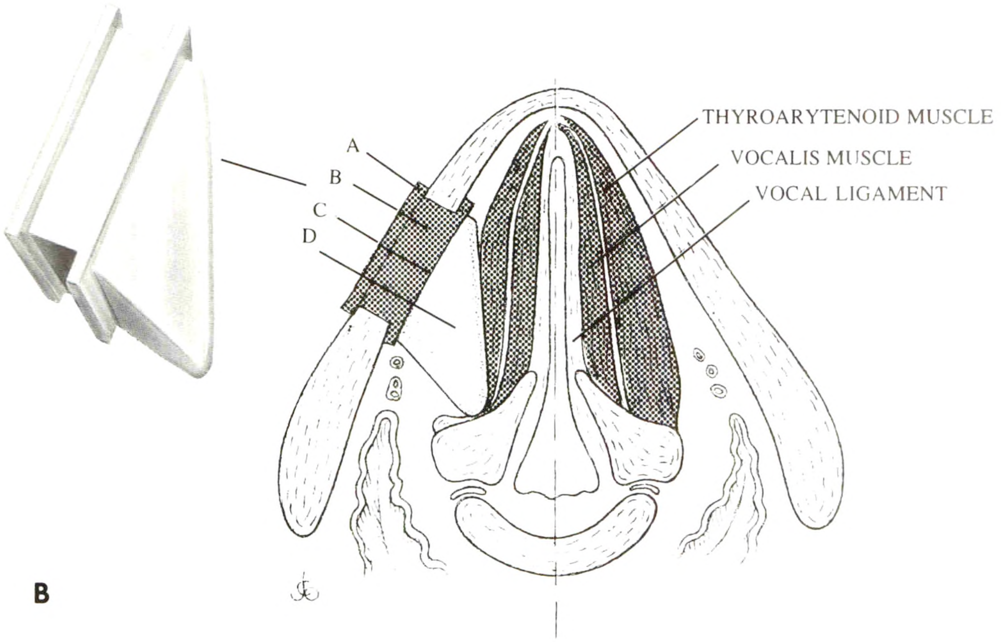


Fig 1. Description of Thyroplasty Implant. Montgomery® Thyroplasty Implant consists of two components: tiered base and obtuse triangular top (A). There are five sizes for both male and female larynges. Difference in size relates to various heights of triangular portion of implant. Tiered base remains constant in all male and all female implants. Base of implant is made up of three tiers (Inset and B): A — Lateral portion of base remains outside thyroid cartilage on its surface. B — Middle portion of base stabilizes implant against any movement and is same dimension as window in thyroid lamina. C — Medial portion of base remains inside thyroid lamina. This design prevents outward displacement of implant. Base is designed for long-term implantation and is constructed from firm-grade silicone. D — Triangular intralaryngeal portion of thyroplasty implant is designed to displace vocal cord medially in order to improve phonation. Height of this portion varies in size according to sex of patient and how far vocal cord is to be medially displaced. Posterior portion projects slightly posteriorly in order to reach base of vocal process of arytenoid. Medial margin of triangular intralaryngeal portion is rounded in order to reduce any potential trauma to vocal cord. Effective height of triangle varies depending on size of implant. Heights for female implants are 6, 7, 8, 9, and 10 mm. Heights for male are 8, 9, 10, 11, and 12 mm. Lateral aspect (base) of triangular intralaryngeal portion adheres to medial tier of base. For female implant, this dimension is 5 × 10 mm, and for male implant, 7 × 12 mm. Obtuse triangular intralaryngeal portion is constructed from softer radiopaque silicone suitable for long-term implantation. Contralateral vocal cord shown here is in position of adduction.

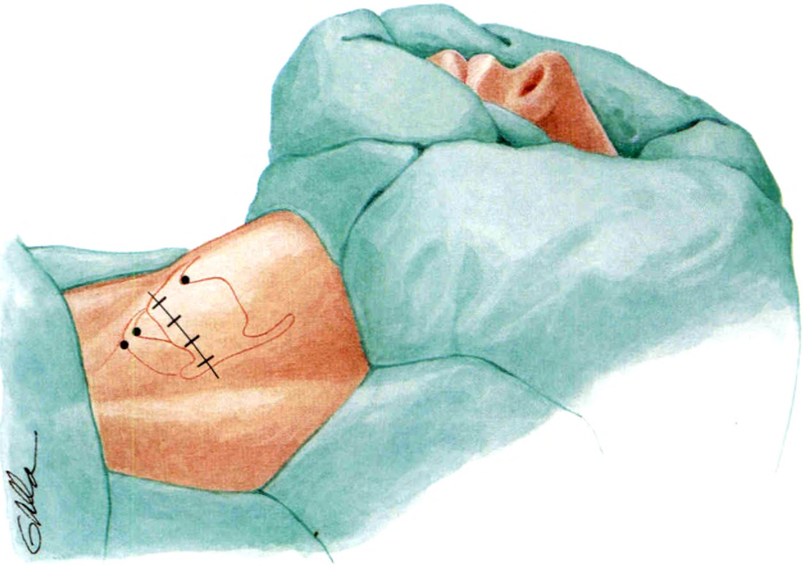


Fig 2. Draping and incision. Patient's anterior neck is prepared and draped so as to expose ipsilateral and contralateral sides. Face remains exposed. Oxygen can be administered to patient by placing tubing under head drapes. Thyroid notch, cricothyroid membrane, and inferior margin of cricoid cartilage (dots) are marked. Horizontal incision is marked approximately 0.5 cm above inferior margin of thyroid cartilage. Area for incision, as well as deep tissues, is infiltrated with 1% Xylocaine with 1:100,000 epinephrine. Incision begins 2 cm from midline on contralateral side and is extended on ipsilateral side of neck to anterior border of sternocleidomastoid muscle. Hatch marks are made so that accurate approximation of incision can be accomplished.

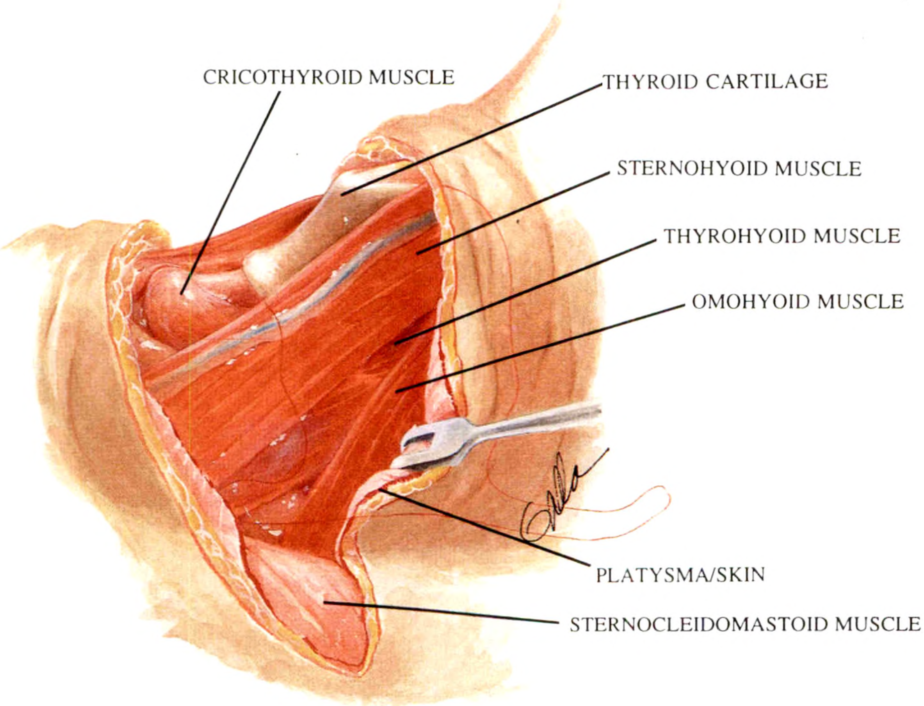


Fig 3. Skin incision is extended through platysma layer so as to expose sternohyoid and omohyoid muscles. Flaps are established superiorly and inferiorly in plane superficial to fascia covering these strap muscles. Flaps are separated with self-retaining retractor. Midline (medial raphe) is identified, and two sternohyoid muscles are separated to expose thyroid notch, anterior aspect of thyroid cartilage, cricothyroid membrane, and cricoid cartilage. Undersurfaces of ipsilateral sternohyoid and omohyoid muscles are dissected so that they can be retracted laterally (Gelpi retractor). If there has been much scarring from previous surgery, it may be necessary to transect these muscles in order to obtain adequate exposure.

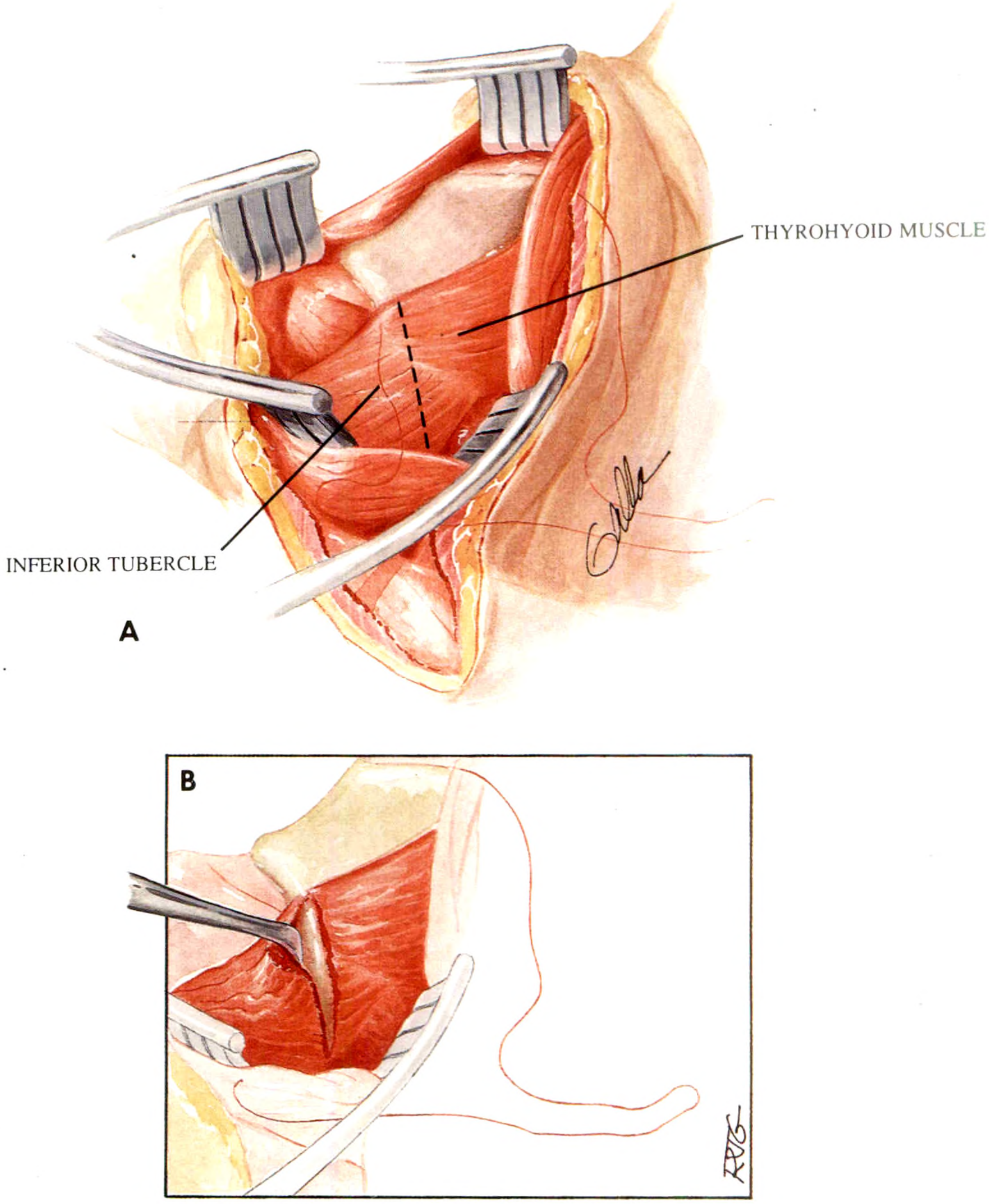


Fig 4. Exposure, continued. A) Strap muscles are retracted laterally to expose thyrohyoid muscle on surface of thyroid lamina. Muscle is transected just above inferior border of thyroid lamina. B) Thyrohyoid muscle is detached from its inferior attachment by means of sharp dissection or cutting current on cautery. Thyroid lamina, its inferior border, and inferior thyroid tubercle are exposed.

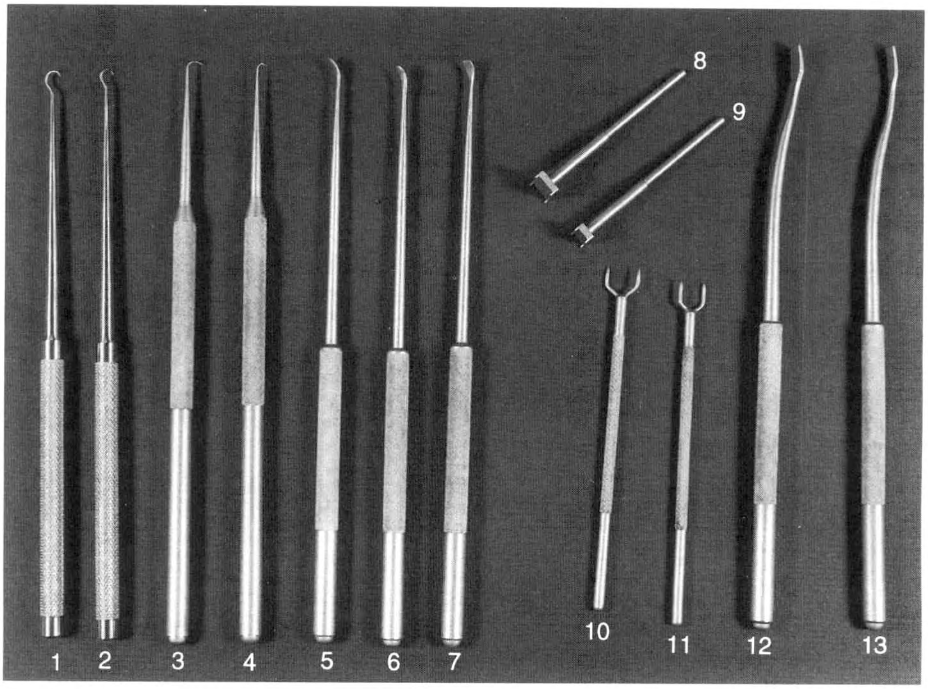


Fig 5. Instruments used for medialization laryngoplasty. Instruments 1 and 2 — Curved Hooks; hooks used for traction on thyroid cartilage. Instruments 3 and 4 — Sharp Hooks; small and large hooks used to elevate cartilage from thyroplasty window. Instruments 5 and 6 — Duckbill Elevators; male and female instruments to elevate inner perichondrium from thyroid cartilage. Instrument 7 — Chisel Elevator; sharp chisel used to separate inner perichondrium from cartilage. Instruments 8 and 9 — Window Outline Instruments, male and female. Instruments 10 and 11 — Window Calipers, male and female. Instruments 12 and 13 — Implant Inserters; instruments for final insertion of implant (male and female).

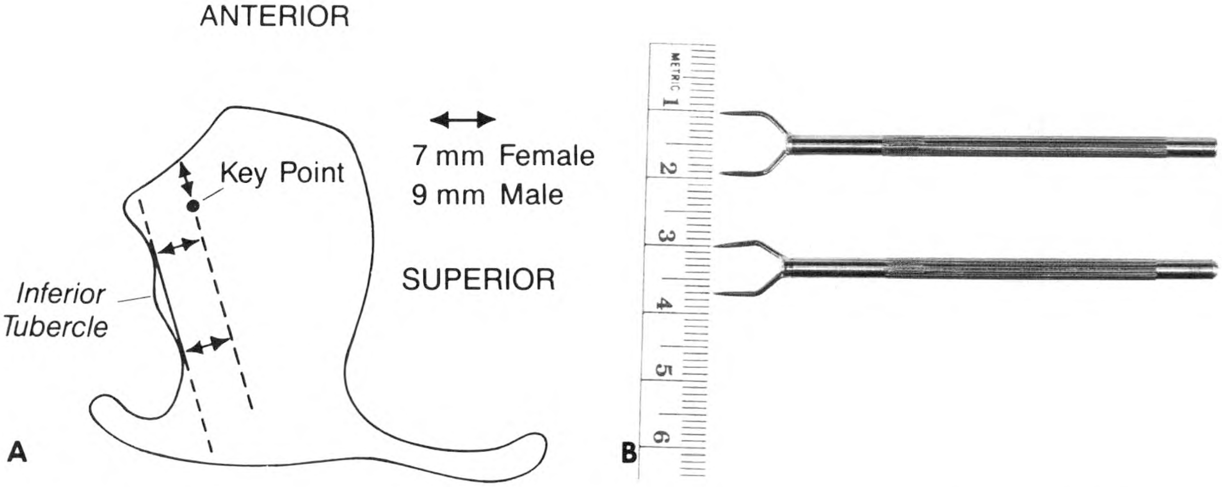


Fig 6. Window Caliper. A) Orientation of window in thyroid lamina. Window Caliper is used to measure from inferior border of thyroid cartilage, anterior and posterior to inferior thyroid tubercle, to superior border of thyroplasty window. It also measures distance from anterior midline of thyroid cartilage to anterior-superior angle (key point) of thyroplasty window. B) Photograph of Window Caliper. Distance between tines of Window Caliper is 7 mm in female and 9 mm in male.

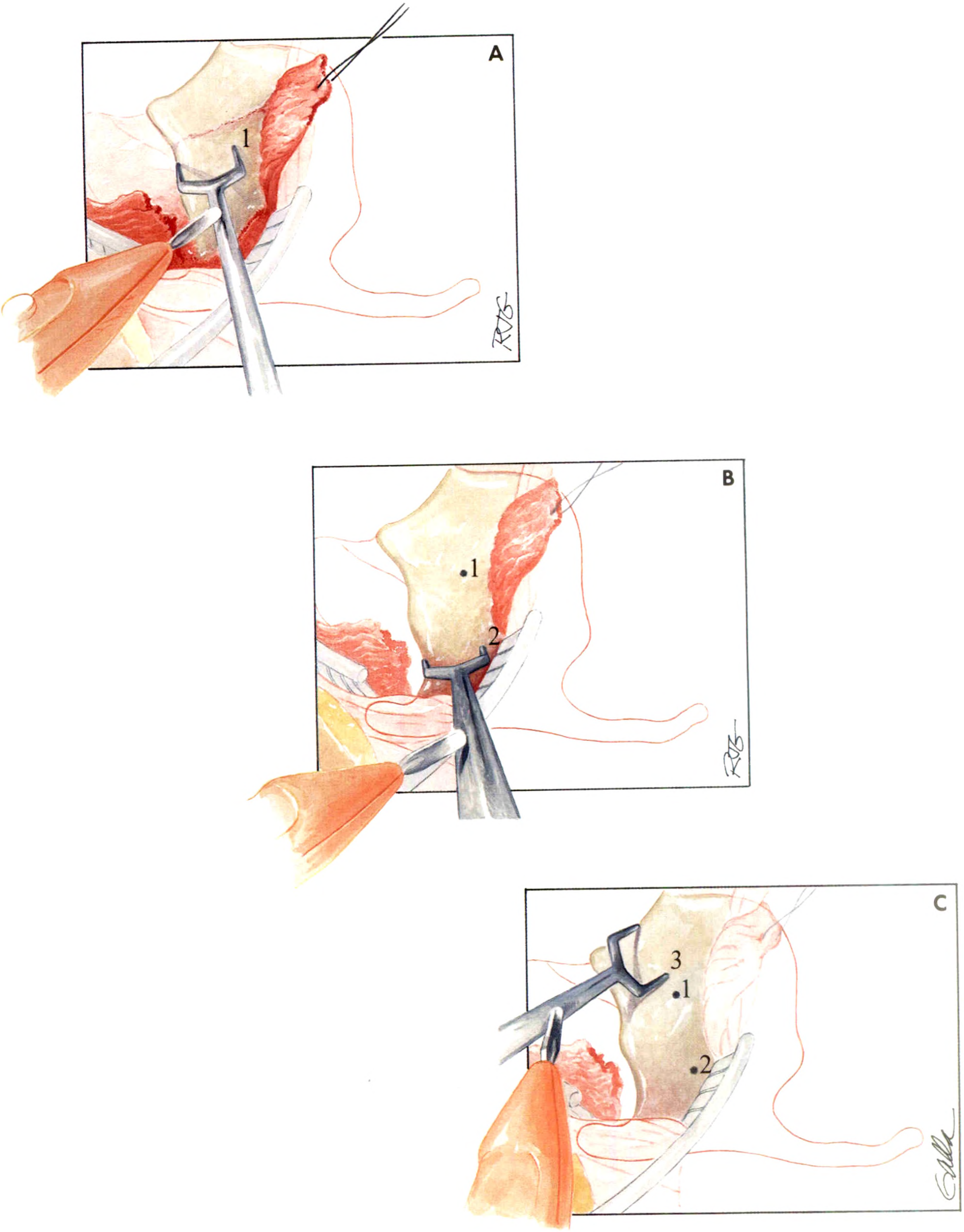


Fig 7. Window Caliper, continued. A) Measuring from inferior border of thyroid lamina, anterior to inferior thyroid tubercle, to point (1) that is to be superior margin of thyroplasty window. B) Measuring from inferior border of thyroid lamina posterior to inferior thyroid tubercle (2). Points 1 and 2 are connected with surgical marker to identify superior margin of thyroplasty window, and also direction of vocal cord. C) Measuring from anterior midline, along line 1-2, to find key point (3) that represents anterior superior angle of thyroplasty window. (See Fig 6A.)

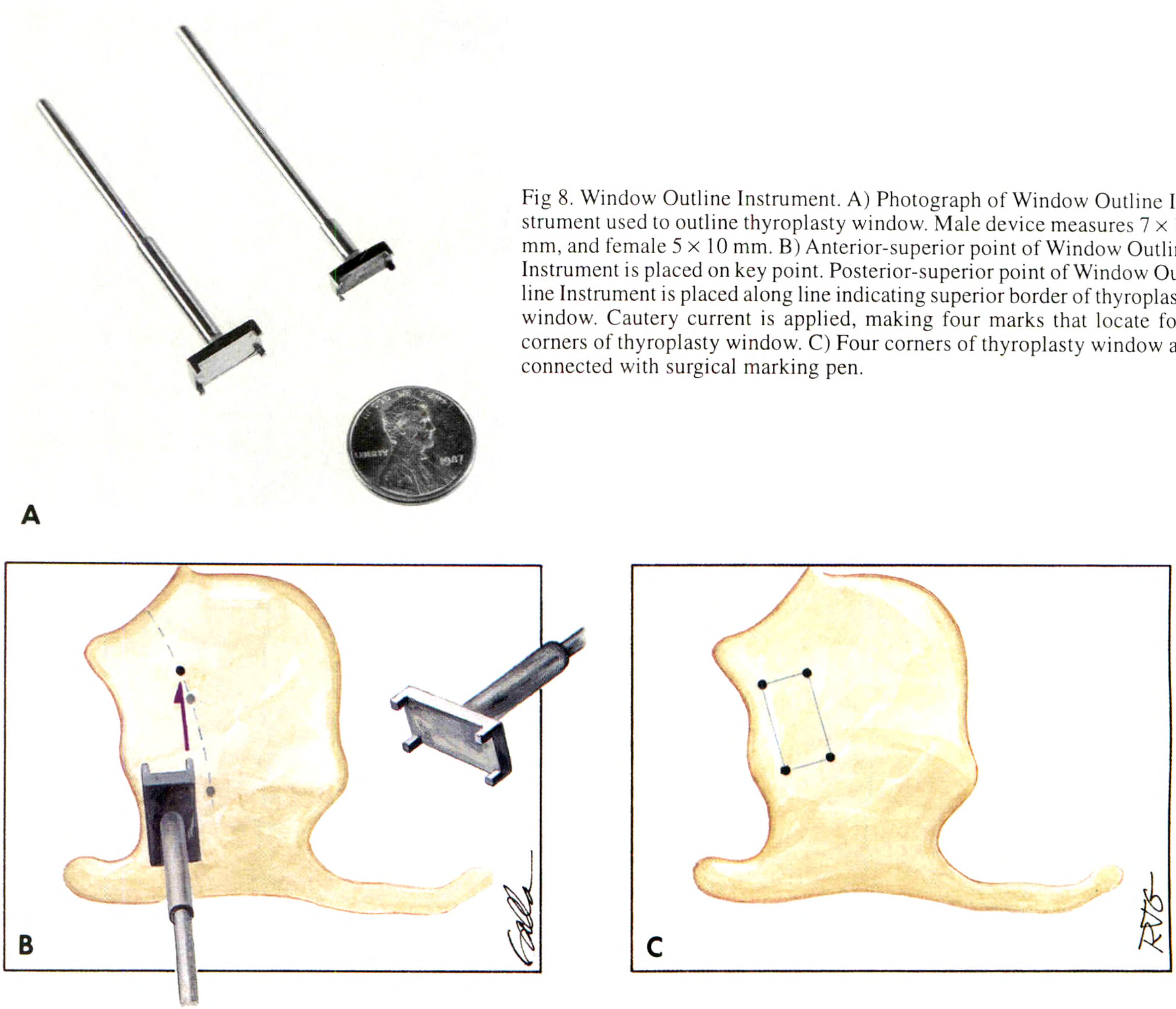


Fig 8. Window Outline Instrument. A) Photograph of Window Outline Instrument used to outline thyroplasty window. Male device measures 7 × 12 mm, and female 5 × 10 mm. B) Anterior-superior point of Window Outline Instrument is placed on key point. Posterior-superior point of Window Outline Instrument is placed along line indicating superior border of thyroplasty window. Cautery current is applied, making four marks that locate four corners of thyroplasty window. C) Four corners of thyroplasty window are connected with surgical marking pen.

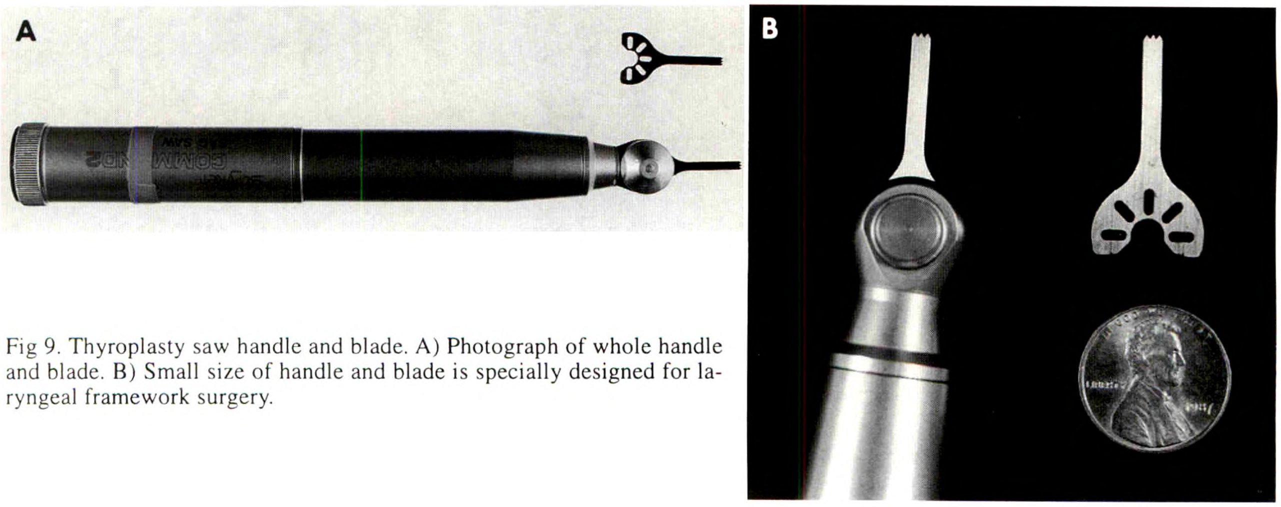


Fig 9. Thyroplasty saw handle and blade. A) Photograph of whole handle and blade. B) Small size of handle and blade is specially designed for laryngeal framework surgery.

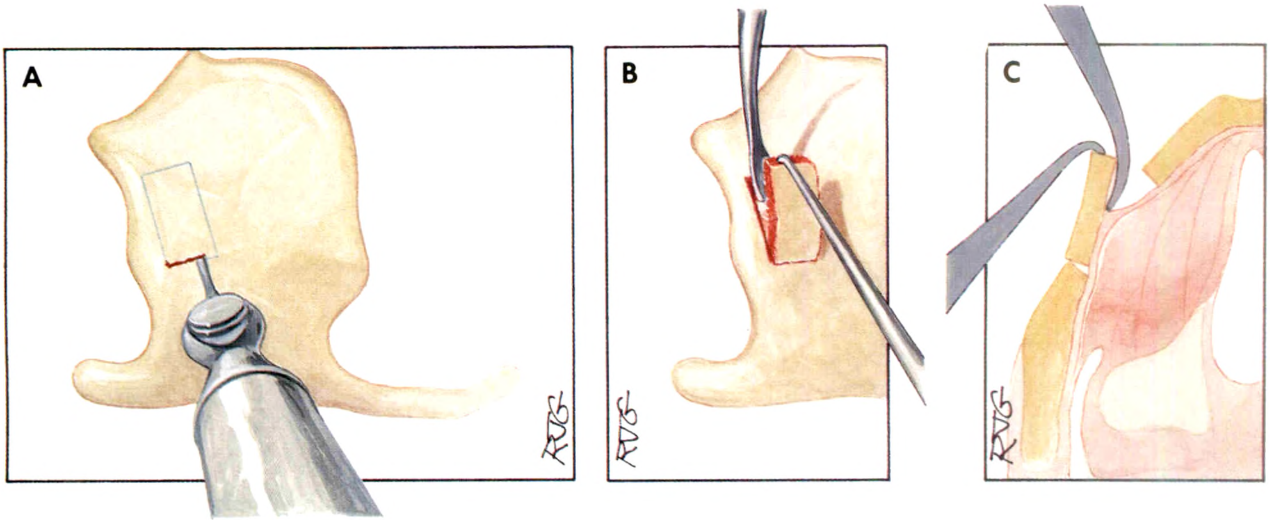


Fig 10. Thyroplasty window. A) Cutting thyroplasty window is done with care so as not to injure underlying soft tissue. It is best to start cutting window posteriorly in case bleeding is encountered. As soon as four sides of window are completely cut, piece of cartilage in window will become loose. B) When piece of cartilage in window becomes loose, its anterior margin is grasped and elevated with small or large Sharp Hook. C) Underlying perichondrium is separated from cartilage.

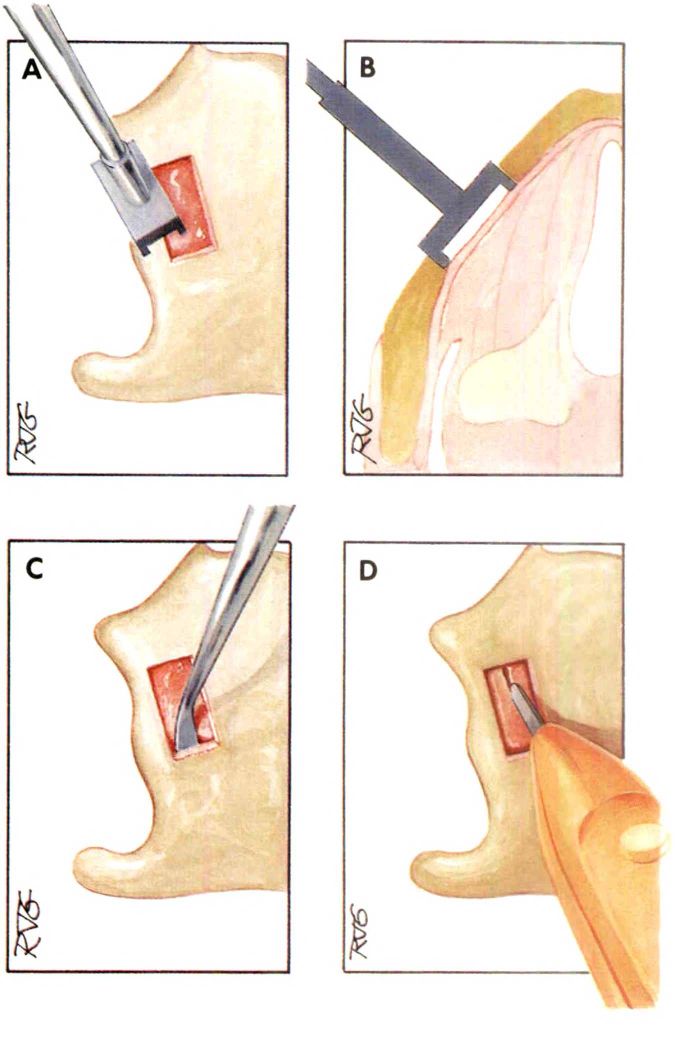


Fig 11. Thyroplasty window, continued. A,B) Window Outline Instrument is inserted into thyroplasty window to make certain it is large enough to admit implant. If window is too small, it can be easily adjusted with thyroplasty saw. Tight fit is ideal. Occasionally, there is bleeding from medullary layer of cartilage. This can be controlled with cautery or bone wax. C) Once cartilage piece has been removed from thyroplasty window, inner perichondrium is elevated from cartilage in all directions. Perichondrium must be elevated posteriorly to level of vocal process of arytenoid. D) Mid-window anteroposterior line is cauterized in inner perichondrium by means of bipolar cautery or Bovie cautery set on low current. This line is carefully incised with knife blade or delicate scissors so that underlying fascia and muscle are not injured.

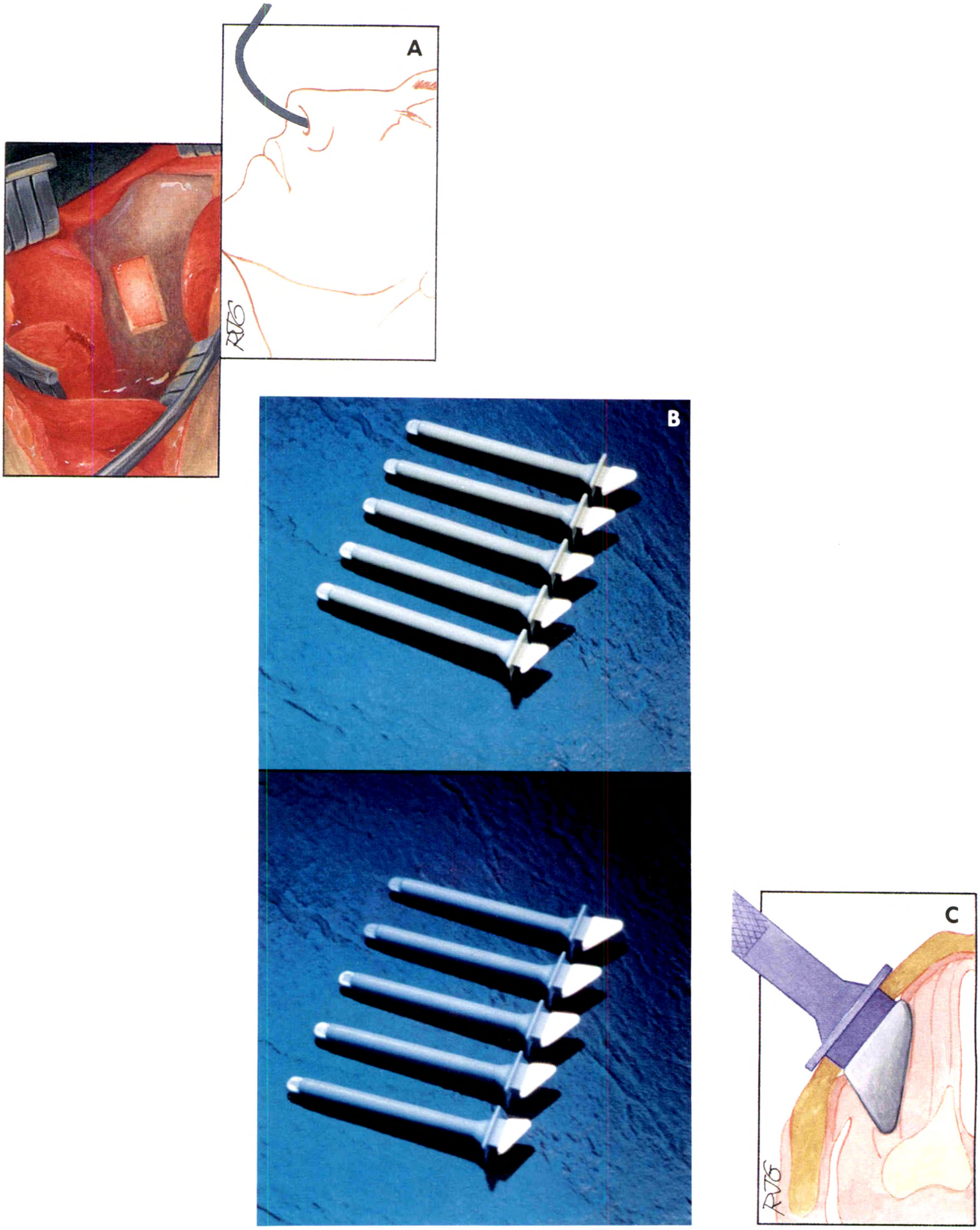


Fig 12. Measuring implant size. A) Larynx is visualized with fiberoptic endoscope by assistant prior to testing with Measuring Device. Soft tissues in window will light up. It may be necessary to cover window while endoscopist becomes oriented. B) Photograph of Implant Measuring Devices. On each handle is imprinted size and gender. Implant Measuring Device sizes are 6, 7, 8, 9, and 10 mm for female and 8, 9, 10, 11, and 12 mm for male. C) Measuring Device is inserted while vocal cords are being observed. Complete closure during adduction and good voice is end point. Ideal measurement is recorded so that correct-size implant can be selected.

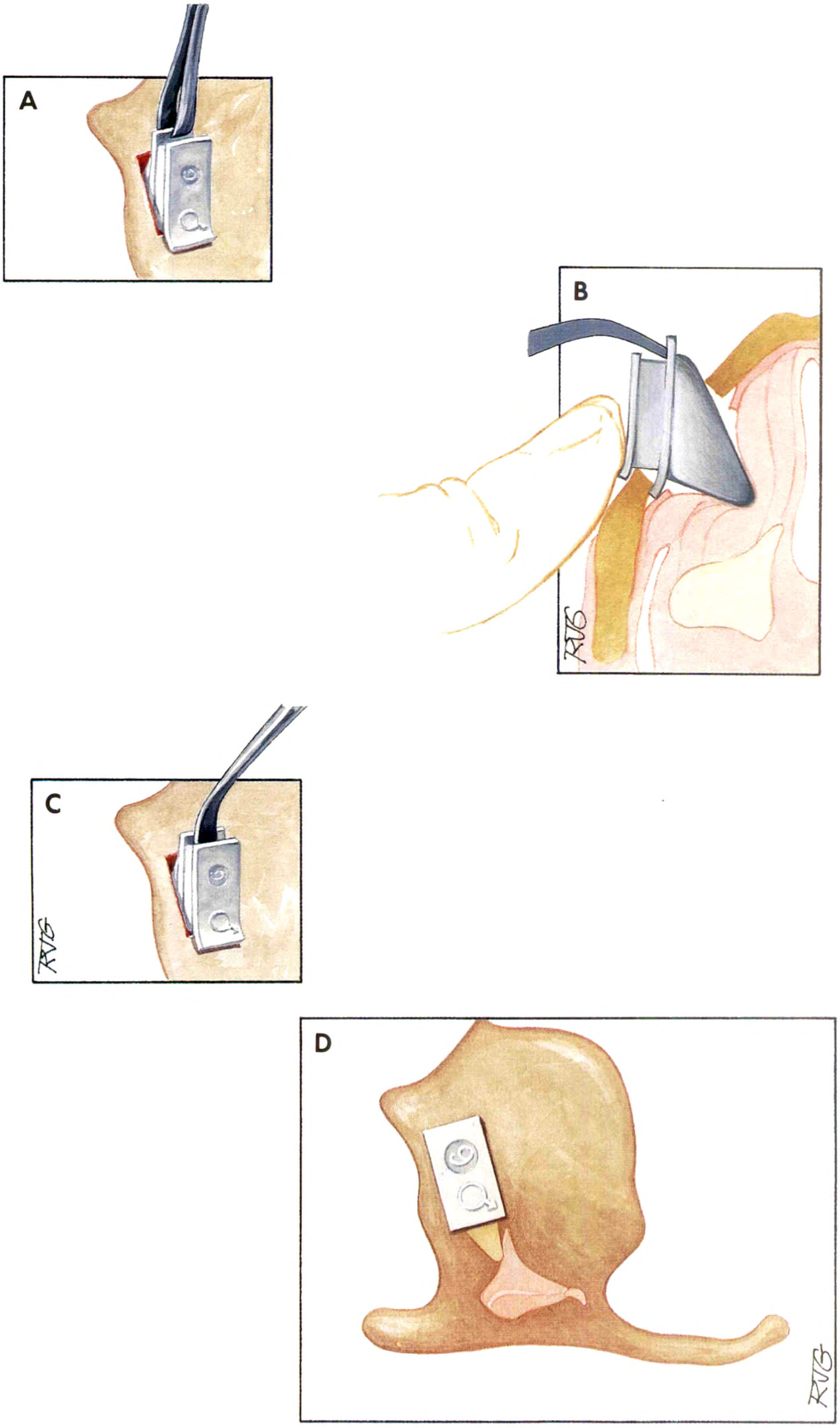


Fig 13. Insertion of implant. A) Lidocaine hydrochloride, 50 to 100 mg, is administered intravenously prior to insertion of implant. Implant is grasped with broad forceps, and posterior tip of triangular portion is inserted through window in direction of vocal process of arytenoid. B) Tiered base of implant is engaged in cartilage rim posteriorly and held there with index finger of nondominant hand. C) Implant Inserter (male or female) is placed in slot anteriorly, and implant is snapped into place. Extra bit of intravenous anesthesia is given prior to this last step, for it can be painful. Vocal cords are again observed during adduction, and voice quality is evaluated. D) Implant in place with its posterior tip against vocal process of arytenoid. Male No. 9 implant is in place.

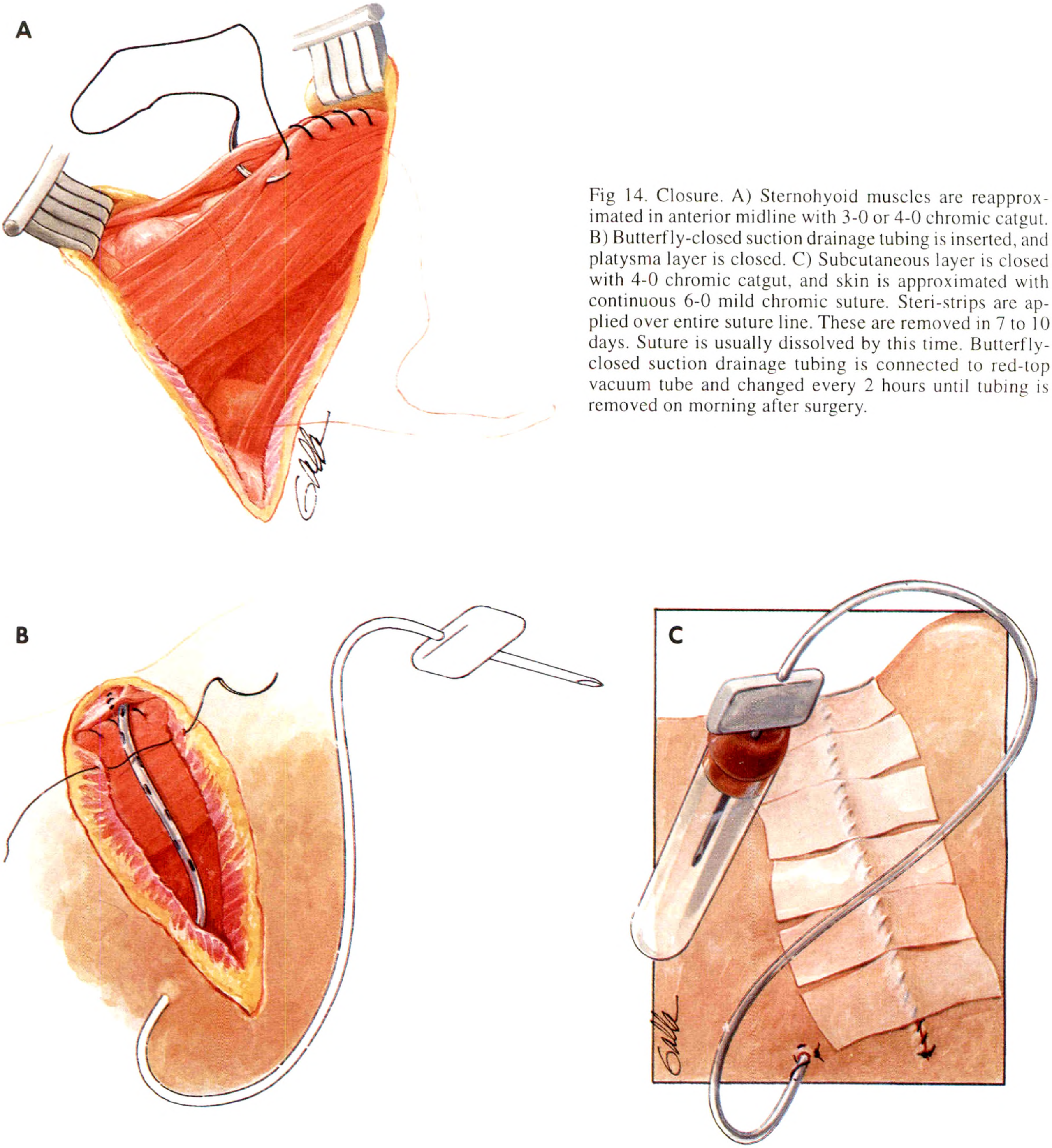


Fig 14. Closure. A) Sternohyoid muscles are reapproximated in anterior midline with 3-0 or 4-0 chromic catgut. B) Butterfly-closed suction drainage tubing is inserted, and platysma layer is closed. C) Subcutaneous layer is closed with 4-0 chromic catgut, and skin is approximated with continuous 6-0 mild chromic suture. Steri-strips are applied over entire suture line. These are removed in 7 to 10 days. Suture is usually dissolved by this time. Butterfly-closed suction drainage tubing is connected to red-top vacuum tube and changed every 2 hours until tubing is removed on morning after surgery.

SUPPLEMENT 171 — OCTOBER 1997
Volume 106, Number 10, Part 2

MEASUREMENT OF AIRWAY PATENCY

A MANUAL FOR USERS OF THE TORONTO SYSTEMS AND OTHERS INTERESTED IN NASAL PATENCY MEASUREMENT

PHILIP COLE, MD, FRCSC
RENATO ROITHMANN, MD
YEHUDAH ROTH, MD
And By Invitation
J. S. CHAPNIK, MD, FRCSC

ANNALS
OF OTOLOGY,
RHINOLOGY &
LARYNGOLOGY

MEASUREMENT OF AIRWAY PATENCY

A MANUAL FOR USERS OF THE TORONTO SYSTEMS AND OTHERS INTERESTED IN NASAL PATENCY MEASUREMENT

PHILIP COLE, MD, FRCSC
RENATO ROITHMANN, MD
YEHUDAH ROTH, MD
And By Invitation
J. S. CHAPNIK, MD, FRCSC

From the Upper Airway Studies Section, Department of Otolaryngology, University of Toronto, Toronto, Canada. Publication supported by the Granovsky Family and Atlantic Packaging in honor of the life of Phil Granovsky as a Canada International Scientific Exchange Program (CISEPO) project.

CORRESPONDENCE — Philip Cole, MD, FRCSC, Gage Research Institute, 223 College St, Toronto, Ontario, Canada M5T 1R4. Fax: (416) 978-2608; phone: (416) 733-8220; e-mail: philcole@msn.com.

COPYRIGHT© 1997, ANNALS PUBLISHING COMPANY, 4507 LACLEDE AVENUE, ST LOUIS, MO 63108

CONTENTS

Foreword. Prof Dr P. A. R. Clement 3

Preface. Philip Cole, MD, FRCSC 3

The Authors 4

Acknowledgments 5

The Canada-International Scientific Exchange Program.
  A Medical Model for International Research, Collaboration, and Service
  Arnold M. Noyek, MD, FRCSC 6

Introduction 7

  The Current Status of Objective Nasal Patency Assessment 7

  Methodology of Current Nasal Patency Tests 7

  The Toronto Rhinomanometry System 8

  The Toronto Acoustic Rhinometry System 9

Rhinomanometry 9

Acoustic Rhinometry 11

Calibration 12

A Diagnostic Nasal Laboratory Session 13

  Acoustic Rhinometry 13

  Rhinomanometry 14

Pros and Cons of the Two Toronto Methods 16

Additional Applications of the Toronto Systems 18

Validation 19

Description and Sources of Equipment 20

The Place of Objective Testing in Clinical Rhinology
  J. S. Chapnik, MD, FRCSC, by invitation 22

FOREWORD

For medicolegal purposes, preoperative and postoperative documentation, nasal challenge tests, and physiological studies, an objective assessment of the upper airway is mandatory.

Ventilation is one of the most important nasal functions, and since the introduction of pneumotachographs with adequate characteristics and sensitive pressure transducers, it has been possible to study nasal patency by dynamic rhinomanometry. Recently, a new method, acoustic rhinometry, was developed to measure static parameters such as cross-sectional areas of the nasal cavity and nasal volume. The two methods are complementary and give important objective information concerning the upper airway.

In view of these developments, the publication of a practical manual for appropriate use of rhinomanometry and acoustic rhinometry will be welcomed by clinicians and basic researchers working in this field. Moreover, as the manual is written by clinical scientists who have long and extensive experience in upper airway research in a center of excellence such as the Upper Airway Studies Section of the Department of Otolaryngology, University of Toronto, this is a guarantee of quality. In this manual one finds not only the indications and limitations of both rhinomanometry and acoustic rhinometry techniques, but also practical tips for everyday use and calibration. As the need for objective assessment of the upper airway is increasingly felt, this manual comes at the right time, and I am sure that in future it will be a frequent source of reference for otolaryngology specialists, plastic surgeons, allergologists, and many other scientists.

Prof Dr P. A. R. Clement
Chairman, International Standardization Committee
on Objective Assessment of the Nasal Airway
Secretary, International Rhinologic Society
Department of Otolaryngology, Head and Neck Surgery
A.Z.-Free University of Brussels
Brussels, Belgium

PREFACE

This manual is written principally for users and prospective users of the Toronto Systems for evaluation of upper respiratory airway patency and is concerned mainly with clinical assessment of the nasal segment of the airway by rhinomanometry and acoustic rhinometry. It is the intention of the writers to provide practical support to those who use the Toronto Systems, guidance to those who are contemplating entry into the field of nasal patency measurement, and suggestions that may be of use to other workers.

The systems described were developed in the Gage Research Institute and the Otolaryngology Departments of the University of Toronto Teaching Hospitals (St Michael's Hospital, Hospital for Sick Children, Mount Sinai Hospital, and Sunnybrook Medical Centre). They embrace the broad principles employed by other workers in the field of upper airway patency studies, and it is the authors' hope that additional features we have incorporated to improve reliability and convenience will be of general interest.

Development of computer processing, quality hardware, and measures to minimize instrumental invasiveness contribute substantially to the objectives of reliability and convenience, and as new technological advances become available, their applicability to upper airway studies is investigated. Results of several years' experience with airway patency measurements in many thousands of subjects are embodied in the contents of the manual.

Philip Cole, MD, FRCSC
Professor, Department of Otolaryngology
University of Toronto
Toronto, Canada

THE AUTHORS

Philip Cole, MD, FRCSC
Professor and Director of Upper Airway Studies
Department of Otolaryngology
University of Toronto
Toronto, Canada

Renato Roithmann, MD
Professor, Department of Otolaryngology–Head and Neck Surgery
Universidade Luterana do Brasil-ULBRA
Canoas-RS, Brazil

Yehudah Roth, MD
Director, The Institute of Nose and Sinus Therapy and Clinical Investigations
The Edith Wolfson Medical Center
Tel Aviv University, Sackler School of Medicine
Holon, Israel

J. S. Chapnik, MD, FRCSC (by invitation)
Associate Professor of Otolaryngology; Active Staff; and Director, Saul A. Silverman Airflow Laboratory and Clinical Investigation Unit
Mount Sinai Hospital
Toronto, Canada

The fellowships of Drs Roithmann and Roth were sponsored by the Isabel Silverman Canada International Scientific Exchange Program (CISEPO). Their researches were undertaken mainly in the Saul A. Silverman Family Foundation Nasal Airflow Laboratory and Clinical Investigation Unit, Mount Sinai Hospital, Toronto, Canada.

ACKNOWLEDGMENTS

This manual contains a compilation of several years of research and development in the field of upper airway studies. The authors acknowledge with thanks the efforts and enthusiasm of the preceding 17 fellows and graduate students from eight different countries who have been attracted to and have given unstintingly to this program of study and research at the University Department of Otolaryngology, Toronto, since the early 1980s. Many have acquired higher degrees, academic appointments, and senior research posts on return to their own countries. The coauthors are examples.

The program was introduced and is directed by the senior author, Professor Philip Cole, whose work has been generously aided by colleagues in the Toronto Teaching Hospitals and in the University disciplines of otolaryngology, respirology, biomedical engineering, and many others, not least by Associate Professor J. S. J. Haight, biomedical engineer Victor Yap, and members of the Gage Research Institute. They all have maintained essential practical support and provided funds, facilities, and laboratory space over the years.

The coauthors, from Brazil and Israel, are the most recent fellows to complete a 2-year program of research. They keep up the traditional overseas connection and were the first researchers to produce peer-reviewed articles, concerned mainly with acoustic rhinometry, from the newly inaugurated Saul A. Silverman Nasal Laboratory and Clinical Investigation Unit of the Otolaryngology and Respirology Departments at Mount Sinai Hospital.

Currently, there are four (three adult and one pediatric) clinical-research nasal laboratories and two private rhinomanometry centers in Toronto, seven in other Canadian cities, and seven in other countries. All employ the Toronto Rhinomanometry System described in the manual. The Acoustic Rhinometry System is used in three Toronto centers. It is in regular use for clinical assessments in the Mount Sinai Hospital Nasal Laboratory. The combined Toronto laboratories provide a clinical service for more than 2,500 patients annually, and research fields are expanding exponentially.

The authors also thank Dr Arnold Noyek, Otolaryngologist-in-Chief, Mount Sinai Hospital, who, as Executive Director of CISEPO, has recognized the international and interhospital collaboration of the Upper Airways Study Program. He has noted that it reflects the aims and objectives of his colleagues, his department, the Non-Government Organization (CISEPO), and the benefactors who provide support. Support for the cost of publication of this manual as a supplement to the *Annals of Otology, Rhinology & Laryngology* was made possible by a generous grant from the Granovsky family. We invited Dr Noyek to outline the history and aims of CISEPO.

THE CANADA-INTERNATIONAL SCIENTIFIC EXCHANGE PROGRAM

A MEDICAL MODEL FOR INTERNATIONAL RESEARCH, COLLABORATION, AND SERVICE

ARNOLD M. NOYEK, MD, FRCSC

The Canada-International Scientific Exchange Program (CISEPO) has as its primary objectives to enrich academic medicine and health care in Canada and internationally, and to contribute to peace-building in the Middle East. CISEPO's results are obtained through scientific exchanges, joint research, and clinical programs among Canadian and international scientists and physicians. During the past decade, the relationship between Canadian and international scientists has flourished.

CISEPO is a nonprofit, charitable program. Grants and foundation benefactions are applied as seeding for peer-reviewed research, industrial sponsorships, and self-funding clinical and research fellowships. Core funding is provided by the Saul A. Silverman Family Foundation.

CISEPO was initiated in 1984 by the Department of Otolaryngology at Mount Sinai Hospital, University of Toronto, Canada, as a formalized, interactive, scientific program between Canada and Israel. Building on its success, CISEPO undertook to broaden its international associations and to expand its partnerships. Currently, CISEPO's programs involve Canadian and other international physicians, scientists, and health care professionals from more than 10 countries in the Middle East, Western Europe, South-East Asia, North America, Eastern Europe, South America, and Australasia.

Canadian involvement in CISEPO, in addition to Mount Sinai Hospital and the University of Toronto, includes the Sir Mortimer B. Davis–Jewish General Hospital and McGill University in Montreal, the Baycrest Centre for Geriatric Care in Toronto, McMaster University in Hamilton, and the Royal College of Physicians and Surgeons of Canada. Since its inception, CISEPO's medical and research contributions have included more than 25 textbook chapters, 250 peer-reviewed publications, 500 general publications, and 250 invited lectures and visiting professorships. The productivity of CISEPO's fellows and the success of its internationalism are exemplified by the contributions to and publication of this manual.

The CISEPO program has fostered broad Canadian and international initiatives in research and medical education. The program has offered research prizes, sponsored continuing education programs and international scientific meetings, and facilitated elective programs for undergraduate medical students. Formal relationships have been established with leading medical schools around the world.

CISEPO fellowships have brought many gifted international physicians and scientists to Canada to study, to conduct research, and to develop their knowledge base. After 1 or 2 years in Canada, these fellows return to their countries of origin to transfer knowledge and technology, to contribute to the professional development of their colleagues, and to initiate multidisciplinary interactions in their communities. Many of these physicians and scientists now occupy senior academic and service positions, several with professorial appointments.

The support of the Saul A. Silverman Family Foundation for CISEPO fellows and the Nasal Airflow Laboratory and Clinical Investigation Unit at Mount Sinai Hospital has been instrumental in CISEPO's fellowship program and its research in rhinology. CISEPO also acknowledges the gracious support of the Granovsky family and of Atlantic Packaging for making the publication of this manual possible.

CORRESPONDENCE — Arnold M. Noyek, MD, FRCSC, Executive Director, Isabel Silverman CISEPO Program, Otolaryngologist-in-Chief, Mount Sinai Hospital, Professor of Otolaryngology, Professor of Medical Imaging, University of Toronto, 401-600 University Ave, Toronto, Ontario, Canada M5G 1X5. Phone: (416) 586-8560; fax: (416) 586-8600; e-mail: cprato@mtsinai.on.ca.

MEASUREMENT OF AIRWAY PATENCY

INTRODUCTION

THE CURRENT STATUS OF OBJECTIVE NASAL PATENCY ASSESSMENT

In addition to their contribution to research, benefits of objective testing to clinical assessment and to patient care are undeniable. Objective testing aids diagnosis, provides a guide and monitor for therapy, helps avoid inappropriate treatment, assists outcome studies, and furnishes medicolegal documentation. It is of increasing importance, also, to the role of third-party payment for provision of medical services. In an expanding number of cases in Canada and the United States, third parties demand confirmation of diagnosis and need for treatment by means of objective tests before agreeing to accept responsibility for payment.

As with other clinical disorders, in addition to being assessed by history and physical examination, nasal dysfunction can be assessed objectively. Nasal patency assessment is widely employed as an important test of nasal function, and international standards are becoming accepted and applied. In Ontario, the provincial health service (OHIP) to 10 million Canadians has an agreed fee for the Toronto System of rhinomanometry, and in many cases in which surgery is proposed for relief of nasal obstruction, OHIP requires rhinomanometric confirmation of the clinical findings before sanctioning payment. As yet, there is no agreed OHIP fee for the more recently introduced acoustic rhinometry test; nevertheless, we have employed it as a useful supplement to rhinomanometry in more than 1,000 cases during the last 4 years.

Following a brief review of general principles, this manual emphasizes the Toronto experience with both rhinomanometry and acoustic rhinometry in diagnosis and management of nasal diseases and in exploration of nasal respiratory function. A short discussion of the research application of the techniques to other upper airway segments is included.

METHODOLOGY OF CURRENT NASAL PATENCY TESTS

Principles of the methods described in this manual are employed for objective assessment of patency of designated segments of the respiratory airways between the nostrils and the carina. The nasal cavities, oral cavity, pharynx, larynx, and trachea have all been investigated in Toronto and in other centers by application of these principles.

Evaluation of patency of the nasal airways is the main concern of this manual. Such assessments are performed widely in both clinical practice and research, and the two principal methods of evaluation in current use employ 1) a dynamic technique (for measurement of both respiratory airflow and differential pressures between proximal and distal extremities of a designated airway segment and derivation of resistance from their ratio $R = \Delta P/V$) and 2) a static technique (for measurement of lumen dimensions of designated airway segments independently of respiratory airflow).

Application of the dynamic technique to the assessment of nasal patency is termed rhinomanometry. Results are obtained by determination of both airflow (V) through the nasal conduit and its associated differential pressure (ΔP) between the limits of the segment.

During exclusive nasal breathing, respiratory airflow through combined or separate nasal cavities is measured and expressed as either cubic centimeters, milliliters, or liters per second. Concurrently, differential pressures are determined between the anterior and posterior nares and expressed as either centimeters of water or the SI (Système International) unit of pascals.(1.0 cm H_2O closely approximates 100 Pa). The procedure is termed active rhinomanometry.

The ratio between differential pressure and airflow ($\Delta P/V$) is termed resistance (R). It is the most widely used measure of how hard it is to breathe through the nose (or other airway segment) and is commonly expressed as centimeters of water per liter per second or, in SI format as recommended by the International Committee on Standardization of Objective Assessment of the Nasal Airway, pascals per cubic centimeter per second.

For practical purposes, effects on the airstream of small volume, density, and viscosity changes resulting from differences between ambient and airway temperatures and humidities are ignored, and respiratory volumes flowing through all airway segments proximal to the carina are regarded as identical.

The static technique of nasal patency assessment, termed acoustic rhinometry, employs the principle of acoustic reflection. Computer processing of incident and reflected sound signals provides a monitor display of nasal airway dimensions during brief periods of voluntary breath-holding. The displays from instruments of different manufacture (which may employ different algorithms) appear similar, but no direct comparisons have been reported.

In the use of both rhinomanometric and acoustic rhinometric techniques it is essential for the exam-

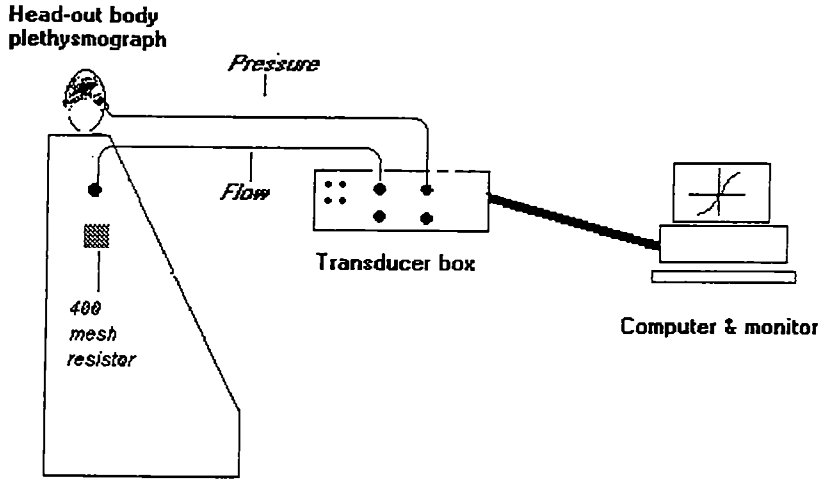


Fig 1. Setup of Toronto rhinomanometry system.

iner to recognize that the main resistor to respiratory airflow is localized to the narrow proximal segment of all normal noses and a large proportion of obstructed noses. A major component of this resistance is situated in the compliant alar segment of the airway, where displacement of mobile tissues by instrumentation introduces a real risk of airway deformation that can lead to unreliable and misleading results. Major artifacts arise from minor interference with airway cross-section, since such alterations affect resistance to airflow exponentially.

In healthy noses, anterior narrowing of the lumen forms the functional nasal valve, which extends several millimeters proximally from within the rigid caval entrance to the caudal end of the upper lateral cartilage (the latter site is known as the anatomical nasal valve) in the compliant alar segment of the airway. The functional valve, which consists of both structural and mucovascular components, creates localized resistance to respiratory airflow that approximately equals the sum of the remaining resistances to the distal limits of the airways.

This narrowed region is the commonest site of nasal obstruction by mucosal swelling, structural abnormality, or a combination of both. Even a minor structural deviation can cause obstruction during the physiological mucosal congestion that accompanies lateral recumbency, the nasal cycle, and environmental exposures. It is of cardinal importance, therefore, that assessment of the patency of this critically vulnerable anterior nasal segment not be compromised by instrumental interference with its compliant portion, which is a major site of resistance in both normal and obstructed noses. Every effort must be made to minimize the invasiveness of the techniques employed, for acquisition of reliable nasal airway data.

Two current methods that risk misleading artifacts are 1) use of a nozzle that can alter nasal lumen dimensions directly by displacement of compliant anterior nasal tissues and 2) use of a face mask that can alter the dimensions indirectly by displacement of adjoining labial and/or other mobile facial tissues. As already mentioned, the resistive consequences of lumen cross-sectional changes are exponential.

Clinical examination is subject to similar shortcomings, since in many noses, insertion of a speculum or manipulation of the nasal tip is necessary to visualize the airway and the mucosa. These maneuvers alter the dimensions of the compliant segment of the nasal airway, which, as noted previously, provides a major contribution to both normal and abnormal nasal resistances, and thus add limitations to the accuracy of a clinician's subjective assessment of patency. Indeed, comparisons between clinical assessments of nasal patency by skilled examiners have shown marked variability. Their assessments also differed from objective measurements, and symptoms show even greater inconsistency.

THE TORONTO RHINOMANOMETRY SYSTEM

The Toronto System of rhinomanometry has been developed in order to avoid inaccuracies that arise from instrumental interference with the respiratory airway portals. It is the method of choice in 20 nasal diagnostic laboratories and research facilities worldwide (1997). In Toronto, in addition to a large number of subjects who undergo experimental investigations, more than 2,500 patients are tested annually in a clinical setting by means of this system.

The system employs a head-out displacement-type body plethysmograph, in which the subject is seated, to measure respiratory airflow. It is used in conjunction with a pernasal catheter to the nasopharynx to measure transnasal differential pressure together with computer-assisted data acquisition and processing, described below in this manual (Fig 1). Although by comparison with a nozzle or a mask, the plethysmo-

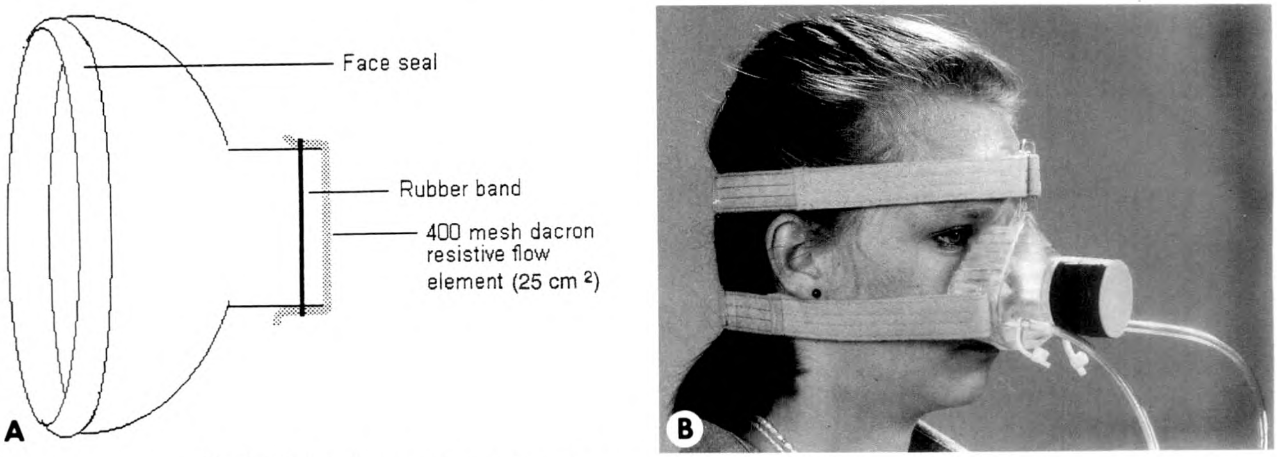


Fig 2. Modified continuous positive airway pressure mask. A) Diagram. B) Photograph.

graph may appear cumbersome, it avoids the very real risk of artifacts as described above. It is simpler in use than a mask. It fits all patients comfortably and independently of size and facial shape. Patients (especially children) prefer it to a mask. It is rugged and easy to calibrate and retains instrumental stability over lengthy periods of time. We have checked the entire data acquisition system weekly over periods of several months with a simulated nasal breathing apparatus (see below), and recording of the results indicates that recalibration is required infrequently.

Regular recorded verification of instrumental calibration with the time and date is essential for maintenance of adequate laboratory standards.

In addition to providing freedom from instrumental interference with the respiratory portals, the head-out plethysmographic method affords unobstructed access to the nasal alar region, enabling the effects of manipulations such as alar retraction on airflow resistance to be determined. The examiner can experiment with resistive effects of elevation of the nasal tip or displacement of neighboring soft tissues and other maneuvers. This ready access to the face has also facilitated visual, video, electromyographic, and other studies of respiratory behavior of the nasal and oral orifices that have been made in our laboratories. Alar retraction (see below, A Diagnostic Nasal Laboratory Session) is an important diagnostic maneuver.

Although the body plethysmograph is mounted on casters and is therefore quite mobile, there are circumstances in which its use is impractical. Since it occupies much more space than a nozzle or a mask, we compromise in field studies and in the sleep laboratory by using a modified continuous positive airway pressure (CPAP) mask incorporating a lightweight pneumotachometer (Fig 2) to measure respiratory airflow in conjunction with the computerized data acquisition method that is employed with the plethysmograph. The CPAP mask provides a soft, comfortable seal with the face. Three sizes are available, and when the mask is applied with particular care, results can be obtained that are reproducible and in close agreement with plethysmograph results.

We use a differently shaped plethysmograph to accommodate subjects in recumbency and for posture studies, but except for brief snoozing periods, we have not yet developed a plethysmograph neck seal suitable for sleeping subjects, since their change in position during lengthy sleeping periods disturbs the integrity of the neck seal.

In our hands, the alternative use of inductive vests, which we find useful for recording thoracic and abdominal breathing of sleeping subjects, has not provided precision in measurement of airflow comparable with that of the plethysmograph or the mask.

THE TORONTO ACOUSTIC RHINOMETRY SYSTEM

Our acoustic rhinometric technique, which has been limited to experience with the Eccovision system, also has been developed to avoid artifacts similar to those described above. Preventive measures include a minimally invasive sound conducting interface between the sound wave tube and the nostril and an adjustable supporting system to stabilize both the acoustic apparatus and the subject's head. (For more information, see Eccovision Operator Manual, E. Benson Hood Laboratories Inc, Pembroke Mass.)

RHINOMANOMETRY

Rhino(rheo)manometry is the measurement of nasal airflow (rheo) and concurrent differential transnasal pressures (mano) as determined during exclusive nasal breathing. The procedure is undertaken to obtain an objective measure of nasal patency to re-

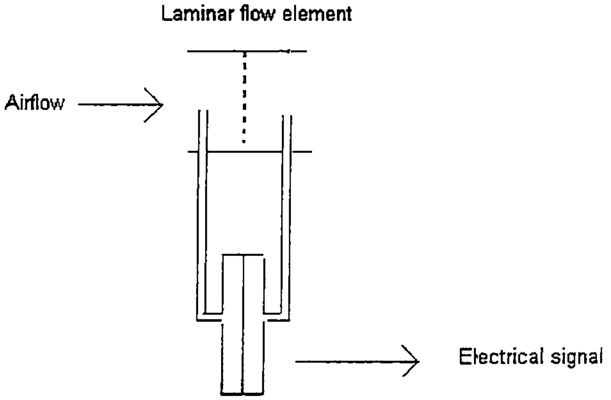


Fig 3. Pneumotachometer. Differential pressure across laminar flow element is conducted to diaphragm of transducer.

spiratory airflow. For diagnostic purposes, it is performed with seated subjects in equilibrium with a comfortable environment, during exclusive nasal breathing at rest.

Airflow is measured by means of a pneumotachometer. This device consists of a laminar flow element of small resistance (400 mesh Dacron filter is used in the Toronto System) in combination with a means of determining the pressure differential between its opposite sides as air flows through it. Since the magnitude of laminar flow through a conduit is directly proportional to the pressure differential between its extremities (Poiseulle's law, V = kP), determination of the pressure differential provides a measure of flow. In practice, pneumotachometer differential pressures are transmitted by tubing to the flexible diaphragm of a transducer. The transducer converts the pressure differential to an electrical equivalent of flow that is measured by electronic means (Fig 3).

A pneumotachometer is commonly incorporated in a face mask (Fig 2) to measure respiratory airflow directly. As an alternative to a face mask (or nasal nozzle), the Toronto System for general diagnostic use employs a pneumotachometer incorporated in the sidewall of a head-out displacement-type body plethysmograph, and respiratory airflow is measured indirectly. As an enclosed subject breathes, an equivalent flow of air is displaced through the plethysmograph pneumotachometer by the subject's respiratory body volume change, and differential pressures between the interior of the plethysmograph and the atmosphere are transduced (Validyne transducer DP 103, Validyne Engineering Corp, Northridge, Calif, has proved to be rugged and reliable in regular use over periods of many years) to electrical signals representing airflow. As noted above, the small volume differences between ambient, nasal, and lung air are ignored.

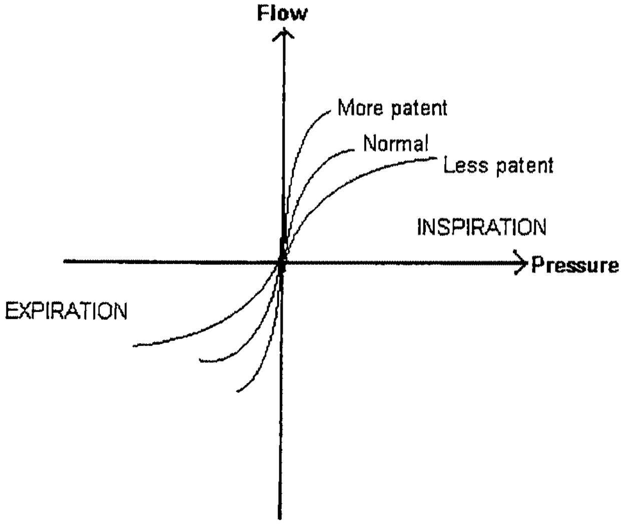


Fig 4. Sigmoid pressure-flow curve.

It should be noted that the displacement-type plethysmograph is much less demanding and simpler in operation than the pressure type that is used in respiratory function laboratories.

Concomitantly with airflow, differential airway pressures are measured by a pressure transducer (Validyne MP 45) via catheters between points in the respiratory airway — in nasal investigation, between the nasopharynx and the atmosphere or, if a face mask is used, between the nasopharynx and the anterior nares. Differential nasal airway pressures are substantially greater than differential pressures between the plethysmograph interior and the atmosphere, and a more sensitive transducer and greater signal amplification are employed for measurement of the latter. The greater sensitivity will be noticed by the operator as calibration is performed.

Signal processing of both airflow and pressure is conveniently achieved by means of transducers as described above. In the Toronto System the resulting electrical analog signals are processed further by digitization. This enables a programmed computer to produce a monitor display of the pressure-flow curve (Fig 4) in real time, and a numeric display of computed nasal respiratory parameters can be obtained on-line. In addition, the options of data storage and hard copy are available.

The digital sampling rate of 50 Hz that is employed provides a measure of both flow and differential pressure approximately 200 times throughout each resting breath, and "averaged resistance" (mean ΔP/V) is computed for any chosen number of breaths. Several concomitant breathing parameters are computed also and can be displayed by selection from a menu of "scientific results." This latter selection differs from the selection of "averaged resistance" in that the current software does not allow the monitor display of results to be saved to disk, but a printout can be obtained on occasions on which a permanent record is required. The "scientific results" display includes breathing frequency, minute ventilation, and tidal volume. In addition, pressure, flow, and resistance values are displayed as averages, as peak values, and at designated points on the pressure-flow curve (eg, 100 Pa, 150 Pa). Work and power of nasal breathing are also displayed.

In the Toronto System, patients breathe spontaneously at rest, and breathing through combined nasal cavities generates transnasal differential pressures of less than 100 Pa. Greater pressures require hyperventilation. Experiments have shown that resistance values calculated either 1) as a computed average, 2) at peak pressure-flow, or 3) at 100 Pa are of similar magnitude in the range below 0.4 Pa/cm^3 per second, and this latter value is well beyond the resistance of combined healthy adult nasal cavities (<0.25 Pa/cm^3 per second). An explanation for the similarities between resistance results obtained by these different methods can be gained from examination of transnasal airflow and/or differential pressure plotted against time. The tracings are not sinusoidal. They show plateaus through much of the breathing cycle that approach 100 Pa, especially in the inspiratory phase. This phenomenon is demonstrated further by the accumulation of data points that can be seen near the extremities of the digitized pressure-flow curve on the monitor screen in the vicinity of 100 Pa during resting breathing. In resting breathing through combined nasal cavities, a differential pressure of 100 Pa is approached but is seldom attained in unobstructed noses; 70 to 80 Pa is more common, even in typically narrow Caucasian noses. Thus, in healthy noses of adult subjects, breathing spontaneously at rest through both nostrils, calculated resistance values fall in a narrow range in which averaged values are the smallest, peak resistances are larger, and resistances measured at 100 Pa are the greatest.

Reliability of measurements is enhanced by averaging a large number of results, and this can be achieved by 1) digitizing the analog signal and augmenting the sampling rate, 2) maximizing the number of breaths included in a measurement, 3) maximizing the number of measurements, and 4) minimizing the coefficient of variation of several measurements.

Experiments with these variables have shown that for clinical purposes, digitizing at 50 Hz and averaging five measurements each of two consecutive regular resting breaths is acceptable, and a coefficient of variation of <8% is easily achieved.

As a measurement is undertaken, the data points of each breath that are displayed on the monitor screen form a sigmoid pressure-flow curve in real time (Fig 4), and when a series of breaths displays regular repetition of the curve, the computerized data acquisition process is activated to sample two consecutive breaths. Irregularity of the sigmoid curve during the sampling period, caused, for instance, by an air leak, a swallow, or a cough, demands cancellation and repetition of the measurement. Each computed resistance value is displayed on the monitor screen, and the procedure is repeated until five values are collected, together with their computed mean and coefficient of variation.

If the coefficient of variation is >8%, the value with the greatest deviation from the mean is deleted and the measurement is repeated until the coefficient of variation is <8%. If greater accuracy is desired, as in some of our research investigations, the system can be readily adjusted to record a larger number of breaths, and a smaller coefficient of variation can be chosen.

ACOUSTIC RHINOMETRY

For allergen challenge investigations and other situations in which mucovascular changes take place over short periods of time, or if avoidance of intubation is desirable, we prefer the use of acoustic rhinometry to rhinomanometry. Acoustic rhinometry is minimally invasive and requires far less time to obtain an evaluation of useful airway parameters than rhinomanometry. It provides an expeditious measure of nasal airway dimensions that include volume of a chosen segment of the nasal cavity in cubic centimeters as a direct measure of mucosal volume change. We use the acoustic method also in assessment of the efficacy of mucosal therapies and in the evaluation of mucosal responses in chamber exposures to the airborne irritants that are found in occupational, indoor, and outdoor environments. In addition to mucosal features, acoustic rhinometry provides information on nasal structure that aids planning and performance of conservative surgery.

In our laboratories, acoustic signals generated in an Eccovision Sound Wave Tube are conducted via an adapter to the nasal cavity under examination. The acoustic signals and their reflections from the nasal cavity are detected by a microphone in the Sound Wave Tube. Resulting electrical signals are processed by an Eccovision programmed computer to provide a graphic display on the monitor screen of a nasal

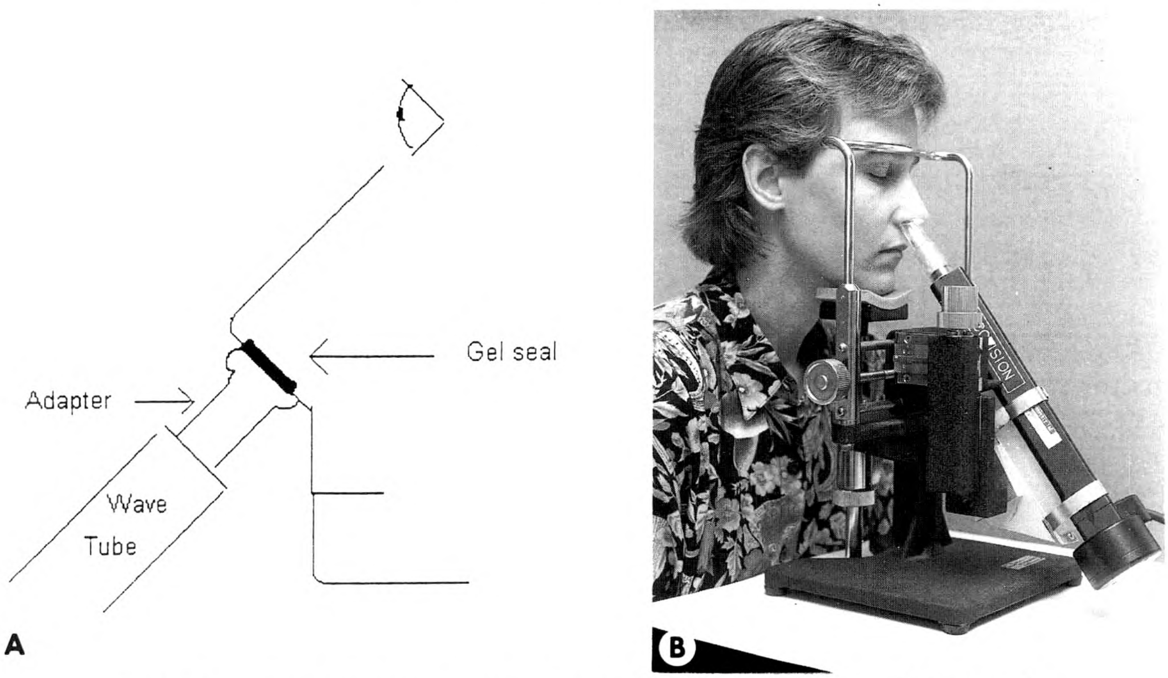


Fig 5. Seal between adapter and rim of nostril (acoustic coupling). A) Diagram. B) Photograph.

cross-sectional area-distance curve and a numeric display of the site and magnitude of minimum cross-sectional area and volume between selected points within the nasal cavity. These parameters quantify important dimensions of nasal airway geometry that contribute to its patency to airflow.

The magnitude of the mucovascular congestion is determined from measurements made before and after application of topical decongestant. Residual resistance is, in most cases, structural, and an alar structural component can be investigated further by means of a spring-loaded plastic strip (Breathe Right) that, by adhesion to the skin overlying the compliant tissues of the anterior nose, dilates the lumen. By means of this spring-loaded device, the length of the functional valve lumen, extending from within the caval entrance to the caudal border of the upper lateral cartilage, is clearly demonstrated in the area-distance graph, and flexibility of alar deformities can be assessed to differentiate between firm scar tissue and structural weakness.

The data are saved to disk and an optional printout provides the clinician with numeric and visual displays of the sites and magnitudes of airway lumen dimensions defined by combined structural and mucosal components. In a clinical diagnostic setting, acoustic rhinometry has provided a useful supplement to rhinomanometric evaluations that have been performed in our Toronto laboratories over the last 4 years.

Reliable and reproducible results are obtained by means of 1) stable and standardized positioning of both the subject's head and the acoustic apparatus, 2) avoidance of displacement of the compliant walls of the anterior nasal airway by use of an appropriately shaped and carefully positioned adapter, and 3) an airtight gel seal in which the gel is applied precisely and generously between the adapter and the nostril rim (Fig 5).

Details of the Toronto techniques employed to achieve these requirements are described below in A Diagnostic Nasal Laboratory Session.

CALIBRATION

Calibration of the acoustic rhinometer is a mandatory preliminary to each series of acoustic measurements, and we do not record it. Attachment of the calibration tube to the Sound Wave Tube enables this procedure to be performed automatically as described in the Eccovision Operator Manual.

The body plethysmograph and its associated data acquisition system are stable and show little change from week to week. Nevertheless, we feel it is good practice to check and, if necessary, to adjust calibration of pressure and flow at weekly intervals and to record the results and the date.

In order to perform a calibration, the monitor display is switched to calibration mode and the zero pressure regulator of the transducer box is adjusted with a fine screwdriver to bring the spot on the monitor to the zero position on the horizontal axis of the display. A pressure signal of 500 Pa (5 cm H_2O) is then applied through connecting tubing to a pressure port of the transducer box by means of a water manometer, and the span pressure regulator is adjusted to bring the spot to the 500-Pa point on the horizontal axis. Zero and 500-Pa positions are rechecked and readjusted as required. The pressure tubing is then connected to the alternative pressure port to confirm that application of 500 Pa of pressure moves the spot to the opposite 500-Pa position.

The zero flow regulator is set to bring the spot to the zero position on the vertical axis. Flow of 1.0 L/s is obtained by means of a regulated hospital wall suction and a rotameter. A vacuum cleaner controlled by a variable AC resistor provides a practical alternative source of airflow. The plethysmograph doors are sealed, the aperture of the rubber dam diaphragm is occluded, and the body plethysmograph interior is connected by tubing to the flow port of the transducer box. The rotameter is also connected to a port in the sidewall of the plethysmograph by wide-bore tubing, and as air is withdrawn at 1.0 L/s, it is replaced by an equivalent flow through the laminar flow element. Zero- and 1.0-L/s flow readjustments are made on the vertical axis of the monitor display by the span and zero flow regulators in a manner similar to the pressure calibration.

If a face mask is used in place of the plethysmograph, as in sleep or field studies, flow calibration is conducted in a similar manner. Air is drawn through the mask pneumotachometer at 1.0 L/s, and differential pressure between the atmosphere and the suction side of the pneumotachometer is transmitted to the flow transducer.

By convention, the inspiratory limb of the pressure-flow curve is in the upper right quadrant of the monitor display. If this is not confirmed as breathing is recorded, the transducer box ports should be reconnected appropriately.

In addition to the calibration methods described above, we regularly check and compare the several body plethysmograph (or mask) data acquisition systems that are in clinical and experimental use in Toronto by means of a portable device that simulates nasal breathing. This device consists of an electrically driven reciprocating piston pump with a 500-mL displacement. The pump drives air through a fixed resistor of similar resistance to the nasal airway at a frequency of 20 strokes per minute. Airflow is delivered to and from the plethysmograph or face mask pneumotachometer by the piston pump through wide-bore tubing, and pressure is generated by flow through the fixed resistor. Flow and pressure simulate nasal breathing, and by connection via the transducer box to the programmed computer, the resistance values and other parameters discussed above are displayed.

This apparatus is useful in determining the need for recalibration, and its repeated use over a period of several years has demonstrated both the stability of our several data acquisition systems and consistent agreement between them.

A DIAGNOSTIC NASAL LABORATORY SESSION

A patient's referral to a Toronto nasal diagnostic laboratory usually results from an examination by a clinician who requires further information about nasal patency as a guide to diagnosis and therapy. In some instances, the information is required for medicolegal purposes, eg, as a pretreatment precaution or for assessment of injury, and it is increasingly requested by health insurance agencies before payment for surgical nasal treatment is sanctioned.

The patient is seated for 20 to 30 minutes to reach equilibrium with comfortable hospital conditions and to reduce the acute effects of exercise and outdoor exposures on nasal mucosal volume. Furthermore, loud ambient sound should be avoided while measurements are being made, since it, too, can affect acoustic results. Demographic and clinical data should accompany the patient, who is requested also to fill out a short questionnaire addressing nasal patency symptoms, which facilitates interpretation of results.

Following a reassuring and suitably detailed explanation of the laboratory procedures to which the patient will be subjected, he or she is seated initially for an acoustic rhinometric test.

ACOUSTIC RHINOMETRY

The Toronto System of acoustic rhinometry is a measurement technique that minimizes displacement of the compliant anterior nasal tissues and thereby contributes to reproducibility of results. We adopt the following procedures.

First, the head of the seated patient is comfortably stabilized in a standardized position by means of a firm stand with adjustable chin and forehead rests.

Second, an adjustable stabilizing device attached to the headrest is employed for the Eccovision Sound Wave Tube, which is connected to the nasal cavity to be tested by means of a plastic adapter. The molded nasal tip of the adapter that conforms approximately with the shape of the patient's nostril is selected from an assortment that includes differently shaped tips.

The stabilized Sound Wave Tube and adapter are aligned parallel with the sagittal plane of the patient's head and at approximately 45° to the palate. They are then carefully adjusted so that the selected adapter is positioned to barely touch the rim of the nostril, thus minimizing anterior nasal deformation. The interface between nostril and adapter is then sealed by generous application of a viscid water-soluble gel (EcoGel 400) expressed from a 5- or 10-mL syringe through a short plastic tube in place of a needle (Fig 5).

Incomplete sealing at the nose-adapter interface is a common cause of an unsatisfactory scan. Irregularity of the scan and the altered sound of the signal are signs of a leak, and the problem can usually be solved by fortification of the seal with additional gel, but occasionally, repositioning with a more suitably shaped adapter is required. It is also possible that a leak may be undetected, and in order to minimize this possibility, generous and precise application of gel is recommended.

In our hands, insertion of nozzles has resulted in larger and much more variable minimum cross-sectional area values than application of an adapter to the rim of the nostril as described above.

Precise manipulation of the Eccovision Sound Wave Tube is facilitated by its light weight and compact dimensions (30 × 4 × 4 cm), and standardized positioning by means of the stabilizing equipment enables reproducible results with a coefficient of variation of <10% to be obtained from repeated tests. We have been unable to achieve equivalent reproducibility with a hand-holding technique.

When the positioning and sealing steps are completed, "Acquire" is highlighted and "Graph Selection" chosen. The patient is instructed to stop breathing for the brief duration of data acquisition. "Enter" is pressed to start data acquisition. A series of rhinographic scans is displayed on the monitor screen, and when a stable display pattern is achieved, it is denoted by an audible signal. "Enter" is pressed to stop data acquisition, and the patient is instructed to resume breathing. The data acquisition procedure is repeated until two minimum cross-sectional area readings are obtained that differ by <10%. Patient and apparatus are then disconnected, and both are wiped free from gel. Following a brief rest, they are reconnected as before, and the procedure is performed again until similarly acceptable results are obtained. The final display is saved to disk, and note should be made on the worksheet of any difficulties.

An acceptable rhinograph displayed on the monitor screen is an area-distance graph. It is a plot of mean values of the concluding series of 10 consecutive rhinographic scans ±1 standard deviation. The horizontal axis of the graph represents distance in centimeters along the curved middle axis of the nasal airway (not the nasal floor). The vertical axis represents the cross-sectional area of the nasal lumen on a logarithmic scale. Numeric values are displayed for minimum cross-sectional area (square centimeters) and its site measured (centimeters) from the nostril along the middle axis of the airway. Nasal volume (cubic centimeters) of a chosen length of the lumen is computed and displayed also.

The accuracy of the parameters decreases with distance along the nasal axis. It also decreases distal to the lumen narrowing. Apparent volume is increased at distances that include the sinus ostia. A length from the nostril of 5 cm is an acceptable compromise for volume measurement. This segment includes the valve (together with any alar and/or septal deformities), almost all the mucovascular tissue of the septum, and much of the mucovascular tissue of the lateral nasal wall, and it avoids posterior cavity and paranasal sinus artifacts.

An optional printout provides the clinician with numeric and visual displays of the sites and magnitudes of airway lumen dimensions defined by combined structural and mucosal components. The mucosal component is usually investigated further by determination of the extent of vascular congestion from measurements made before and after application of topical decongestant.

In some cases (eg, postrhinoplasty nasal obstruction) it is instructive to study the anterior nasal lumen further by a determination of the effect on the area-distance graph brought about by application of a Breathe Right spring-loaded device to the alar region as described above, by which differentiation between firm scar tissue and alar weakness can be made.

Acoustic measurements are performed for each nasal cavity, and when these are completed, rhinomanometry is commenced.

RHINOMANOMETRY

The patient is seated comfortably in the body plethysmograph. The top door of the plethysmograph is closed slowly as the rubber diaphragm is eased carefully (one must beware of earrings) over the patient's head to form an airtight seal around the neck.

The patient is requested to blow the nose clear of mucus and is reassured as a fine catheter is introduced 8 cm along the floor of the nose to the na-

TABLE 1. RHINOMANOMETRIC FINDINGS IN 891 UNOBSTRUCTED NOSES AND CLINICAL GUIDELINES

	Untreated		*Decongested*		
				Unilateral	
	Bilateral	*Unilateral*	*Bilateral*		*Retracted*
Average	0.14	Varies markedly with cycle	0.09	0.23	0.09
Guidelines	0.25		0.15	0.40	0.15

Average of 891 series of rhinomanometric resistance measurements that exclude values exceeding obstructive guidelines. Data are in pascals per cubic centimeter per second.

Note: Decongestion reduces average untreated bilateral resistance by 36% (0.14 to 0.09), indicating average mucovascular component of resistance.

Alar retraction reduces average decongested unilateral resistance by 61% (0.23 to 0.09), indicating that major site of nasal airflow resistance is in compliant alar region.

sopharynx. The catheter is then secured to the upper lip with adhesive tape, and both top and front doors are sealed. Experiments have shown that the presence of the catheter does not obstruct the airway sufficiently to affect measurement values, probably because there is little airflow along the nasal floor, and the catheter rarely causes irritation when in place.

The clinician elevates the nasal tip with the left thumb to visualize insertion of the catheter along the nasal floor. One should avoid hesitation on insertion, as it promotes patient anxiety. The nasal floor is relatively insensitive. In other nasal areas, touch promotes discomfort, sneezing, and secretion. The clinician inserts and fixes the catheter at 8 cm with its distal ports vertical; ensures that all door sealing locks are firmly fastened; and checks the neck seal repeatedly and positions the patient to avoid leaks.

Connection of tubing to the ports of the transducer box is completed (nasal catheter to pressure port and plethysmograph to flow port), and the data acquisition program is activated by pressing "Enter" on the keyboard. If everything is in order, a sigmoid pressure-flow curve is displayed on the monitor screen as the subject breathes through the nose.

Occasionally, the pernasal catheter becomes blocked with mucus, which distorts the sigmoid display, and thus the blockage is readily recognizable. It can usually be cleared by brisk puffs of air delivered through the catheter from a 50-mL syringe while the subject is instructed to hold the mouth open.

Employment of an alternative to pernasal catheterization for measurement of transnasal pressures is in general use in our laboratories for testing children. The method is termed posterior rhinomanometry, and its important purpose is to include assessment of the contribution of the adenoid to resistance of the airway during nasal breathing.

In this method, with lips closed about a large-diameter tube, the patient is instructed to breathe quietly through the nose, to relax the throat (tongue, palate, and pharynx), and to watch the monitor display. When a sigmoid pressure-flow curve is produced on the screen, the patient is encouraged to repeat and maintain the configuration. Children adapt to this feedback technique quite readily — indeed, more readily than adults. The method requires patience and persistence, but contrary to reports in the literature, failure is rare in the hands of an experienced examiner.

The posterior rhinomanometric method is also used in adults when it is necessary to avoid irritation of highly sensitized mucosa by a pernasal tube, as in cases of acute allergy or in the frequently repeated measurements of challenge experiments.

The monitor display of a sigmoid curve consists of about 200 digitized pressure and flow data points in each breath, and since the plethysmograph (flow) and nasal catheter (pressure) signals are slightly out of phase, a loop may be displayed. The system then requires tuning by electronic delay of the pressure signal in order to close the loop and thus obtain a clean sigmoid pressure-flow curve. Tuning is done by pressing and releasing the F2 key together with a numeric key between 2 and 7 on the keyboard while the system is running. The procedure is repeated until a regular, smooth curve results.

When these arrangements are completed, airflow

TABLE 2. EXAMPLES OF TYPICAL RHINOMANOMETRIC FINDINGS

Untreated Sides			*Decongested Sides*					
						Retracted		
Both	*Left*	*Right*	*Both*	*Left*	*Right*	*Left*	*Right*	
0.21	0.40	0.51	0.14	0.26	0.35	0.12	0.15	A
0.37	1.69	0.51	0.10	0.31	0.22	0.14	0.07	B
0.26	0.44	1.02	*0.24*	0.35	*0.96*	0.13	0.15	C
0.25			0.15	0.40		0.15		D

Data are in pascals per cubic centimeter per second. Numbers in italics indicate abnormal values.

A — unremarkable nasal airflow resistances; B — obstructive mucovascular swelling; C — structural obstruction of right airway in its compliant portion; D — guidelines.

resistance measurement can commence. Tables 1 and 2 show results obtained from adult subjects breathing at rest.

Step 1. The first series of measurements is obtained from the combined nasal cavities of the untreated nose. The patient is instructed to breathe quietly, with neither effort nor emphasis, exclusively through the nose.

When the monitor display shows a regularly repeating, smooth sigmoid curve, the data acquisition program is activated by pressing "Enter." In a few seconds a computed resistance value is displayed.

Repetition of the procedure produces a column of five resistance values with a computed mean and coefficient of variation. As described above, if the coefficient is >8%, the column of resistances is examined to note the value with the greatest deviation from the mean. Deviant values are deleted and corresponding measurements repeated until the coefficient is <8%.

"Enter" saves the final result as a mean of five measurements, each of two consecutive breaths.

The result represents the nasal resistance experienced by the patient during resting breathing at the time of the examination. It is therefore prudent to question the patient while he or she is in the plethysmograph about the current severity of the symptoms of which he or she has complained.

It will be noted that with unobstructed noses the peak of the monitor pressure-volume curve approaches, but does not usually attain, 100 Pa when subjects are breathing at rest. In some centers, resistance is measured at 100 Pa, and in others, at 150 Pa; each requires hyperventilation, and since nasal airflow is nonlaminar, increased flow leads to exponentially greater resistance values. Similarly, by comparison with bilateral nasal breathing, the increased linear velocity of flow of unilateral breathing as in steps 2 and 3 below results in exponential elevation of resistance; thus, application of Ohm's law for parallel resistors cannot provide an accurate measure of combined nasal resistance from separate measurements from the two sides.

Step 2. Each nasal cavity is tested separately in a manner similar to step 1, while the opposite side is gently occluded. Occlusion must be performed with care to avoid vestibular distortion of the patent side. The ball of a gloved thumb is commonly used. A moist cotton ball or adhesive tape are less convenient alternatives.

Resistances of the two sides differ almost invariably. The differences may be due to obstructive abnormalities, but it should be recognized that they are dependent also on the spontaneous nasal cycle of alternating resistances.

Step 3. The mucosa of each nasal cavity is decongested by application of three sprays of 0.1% xylometazoline hydrochloride, and after a wait of at least 10 minutes, steps 1 and 2 are repeated. (On rare occasions an anomalous congestive response has occurred, and in these circumstances we have used 5% cocaine to achieve decongestion.)

Comparison with results of steps 1 and 2 indicates the extent of mucovascular congestion. Decongestion also abolishes the nasal cycle.

Step 4. Step 2 is repeated while the ala of the unoccluded decongested side is widely retracted. Alar retraction minimizes resistance of the compliant anterior segment of the nose, which exceeds residual resistance of the rigid caval segment in all unobstructed noses and most structurally obstructed noses. Measurements reveal the decongested resistances of the compliant anterior and rigid caval segments of each side. Almost all structural obstructions are present in the compliant alar lumen, and half of them extend to the adjacent cavum.

On completion of the rhinomanometry series, the nasal catheter is removed, and to conclude the nasal patency assessment, acoustic rhinometry is repeated while the nasal mucosa is decongested (Tables 1-5).

A printed report of nasal airway resistances and dimensions together with comments is sent by hand, fax, or mail to the referring practitioner.

PROS AND CONS OF THE TWO TORONTO METHODS

When the Toronto Systems are employed, both rhinomanometry and acoustic rhinometry provide objective measurements of nasal patency with minimal invasiveness. Both methods enable sites and magnitudes of structural and mucovascular resistive airway narrowing to be determined. Reproducibility of results has been demonstrated by repeated measurements over periods of several weeks in healthy noses in which the nasal cycle has been abolished by application of topical decongestant. These latter measurements have achieved coefficients of variation of <10% for both rhinomanometric and acoustic rhinometric values (Tables 3-5).

This degree of reproducibility compares favorably with that of other widely accepted laboratory tests, and in our hands the use of nozzles and hand-holding of the acoustic rhinometer have produced less reliable results.

The dissimilar methodologies of rhinomanometry

TABLE 3. VARIATION OVER TIME OF RHINOMANOMETRIC MEASUREMENTS

	Combined Cavities	
Subject	*Rn*	*CoV%*
1	0.078	5.3
2	0.075	8.3
3	0.064	11.6
4	0.070	7.7
5	0.081	6.0
6	0.065	12.1
Mean	0.072	
Over time		8.5

Coefficients of variation (CoV) of rhinomanometric measurements of nasal airflow resistance (Rn in pascals per cubic centimeter per second) of combined nasal airways of six healthy, decongested adult noses measured on five occasions at intervals of 1 to 2 weeks.

and acoustic rhinometry produce results that are not directly comparable, and although acoustic lumen dimensions and airflow resistance values resulting from changes in nasal airway caliber are mutually consistent, they bear no simple statistical relationship. Acoustic rhinometry and rhinomanometry serve different purposes. Neither is a substitute for the other, and they can be complementary.

Rhinomanometry. The advantages of rhinomanometry are as follows.

1. The method informs the investigator of how hard it is for the subject to breathe through the nose in terms of resistance, which is an intuitively recognizable measure.

2. The sensitivity of the method is of a high order, since resistances are related exponentially with the cross-sectional area of the airway.

3. The extent of the mucovascular component can be determined.

4. The resistances of both the compliant alar and rigid caval segments can be determined.

The disadvantages of rhinomanometry are as follows.

1. The method is time-consuming. It requires 20 to 30 minutes to complete a comprehensive diagnostic test.

2. Manipulation and presence of a pernasal catheter in the nasopharynx, as used with adults to measure transnasal pressure, is potentially irritant to sensitive mucosa, but rarely creates a problem in diagnostic testing. Indeed, the catheters are well tolerated overnight in sleep studies. However, they can be a nuisance in challenge tests and in severe inflammatory and allergic states of the mucosa.

3. As an alternative to a pernasal catheter, a mouth tube (as used with children to determine adenoid obstruction) is employed to measure transnasal pressure between the atmosphere and the oropharynx. It is somewhat demanding of patience and persistence for both patient and examiner, but as noted above, failure is rare in the hands of an experienced examiner.

TABLE 4. VARIATION OVER TIME OF ACOUSTIC RHINOMETRIC NASAL CAVITY VOLUMES

	Right Volume		*Left Volume*	
Subject	*cm³*	*CoV%*	*cm³*	*CoV%*
1	4.5	8.1	5.9	11.6
2	5.5	5.1	5.8	7.0
3	5.9	4.7	5.2	4.8
4	6.1	6.2	6.5	12.7
5	6.3	2.5	5.2	3.9
6	6.0	4.3	5.1	3.9
Mean	5.7		5.6	
Over time		5.2		7.3

Coefficients of variation (CoV) of acoustic rhinometric measurements of unilateral nasal lumen volume (0 to 5 cm from nostril) of six healthy, decongested adult noses measured on five occasions at intervals of 1 to 2 weeks.

4. Nasal airflow is nonlaminar, and the pressure-flow relationship is nonlinear. This flow regime is termed transitional; it is chaotic and not amenable to simple mathematic description. Measurements are empirical.

Acoustic Rhinometry. The advantages of acoustic rhinometry are as follows.

1. Its invasiveness is minimal. It avoids dilation or other distortion of the compliant and resistive anterior nose and the need for nasal or oral intubation.

2. The method provides anatomic measurements and graphic display of dimensions of the critically resistive lumen of the anterior nasal airway.

3. Results can be acquired rapidly and repeatedly;

TABLE 5. VARIATION OVER TIME OF ACOUSTIC RHINOMETRIC MINIMUM CROSS-SECTIONAL AREAS

	Right MCA		*Left MCA*	
Subject	*mm²*	*CoV%*	*mm²*	*CoV%*
1	37	15.1	93	4.4
2	57	9.6	63	12.9
3	66	7.0	50	16.7
4	60	7.7	84	3.5
5	76	3.8	65	8.2
6	76	5.1	55	11.5
Mean	63		68	
Over time		8.1		9.5

Coefficients of variation (CoV) and minimum nasal cross-sectional areas (MCA) of six healthy decongested adult noses on five occasions at intervals of 1 to 2 weeks.

thus, measurements of transient mucosal volume changes can be captured, followed, and recorded.

4. Mucovascular volume changes can be quantified in cubic centimeters (despite the disadvantages below). Lumen changes and abnormalities can be identified and assessed with greater precision than by visual inspection.

5. The information is of value in planning and performing precise and minimally invasive surgical procedures in the nasal valve region.

The disadvantages of acoustic rhinometry are as follows.

1. The numeric results do not inform the investigator how hard it is for the subject to breathe through the nose.

2. Accuracy decreases with distance from the nostril. The choana and the paranasal sinuses probably contribute to discrepancies in the posterior cavum.

3. Accuracy decreases distal to a constriction, and noses are constricted in the valve region.

4. Resolution is limited by several practical assumptions in the algorithm, and model experiments demonstrate that absolute dimensions can only be approximated.

Although both Toronto methods achieve similar reproducibility, there are specific circumstances in which one or the other method offers singular advantages.

Rhinomanometry, although time-consuming, is particularly useful in diagnosis, since it indicates to the examiner how hard it is for the patient to breathe through the nose. The magnitudes of resistance of the whole nose, each bony cavum, each compliant anterior segment, and the mucovascular component of resistance are determined. It is a sensitive and widely used method for nasal patency assessment, and the significance of the derived parameter, resistance, is easily understood (Tables 1-3).

Acoustic rhinometry enables rapid and minimally invasive measurements of anterior nasal lumen dimensions to be made. These dimensions define patency to airflow, and in addition, they are particularly useful for recording transient mucovascular changes directly, as for instance, in allergy challenge investigations and in measurement of mucosal responses to airborne irritants. The method provides a primary investigative tool in many of our research projects.

Although limitations of the algorithm produce only approximations of absolute values, changes are readily recognizable. Furthermore, nasal surgeons have expressed appreciation for the graphic representation of airway dimensions and find both the graphic and numeric data to contribute important information for planning and execution of surgical procedures. During the last 4 years, approximately 1,000 of more than 10,000 diagnostic rhinomanometric evaluations have been usefully supplemented by acoustic rhinomanometry in our Toronto nasal laboratories.

ADDITIONAL APPLICATIONS OF THE TORONTO SYSTEMS

Beyond the Nose. Minor modifications of the Toronto Rhinomanometry System enable other upper airway segments to be investigated in a manner similar to that of the nose. For practical purposes, as mentioned above, volumes of respiratory air flowing through each airway segment proximal to the carina can be regarded as identical during exclusive nasal breathing. Thus, measurements of respiratory airflow obtained by means of a pneumotachometer combined with a head-out body plethysmograph or a face mask are applicable to all such segments. By contrast, linear flow velocities and other aerodynamic features, including resistances and differential pressures, differ markedly between segments, resulting in characteristics of physiological interest and clinical importance in each designated segment.

As with the nose, differential pressures between distal and proximal points in other airway segments are measured and recorded via pernasal catheters. These measurements are made by means of the Toronto System, not only in a single airway segment, but in different segments at the same time by using multichannel transducer circuitry.

For example, pernasal catheter measurements of differential pressures are carried out concurrently in the nasal (between epipharynx and anterior nares) and pharyngeal (between epipharynx and hypopharynx) airway segments, as in sleep and posture studies. Furthermore, individual segments can be subdivided (eg, above and below the palate), and the Toronto circuitry also enables as many as four segments to be measured simultaneously. Plethysmograph or mask flow signals and catheter differential pressure signals from designated segments are digitized and processed by the Toronto rhinomanometry software described above, while analog pressure, flow, and other relevant signals can be relayed concurrently to a chart recorder in sleep, snoring, and posture studies.

Thus, in addition to rhinomanometry, investigations regularly undertaken in our laboratories include measurements of transmural pharyngeal pressures generated by breathing through resistive nasal cavities, pharyngeal aerodynamics associated with orthopnea, hypopnea, and snoring in sleeping subjects, and effects on pharyngeal aerodynamics of posture and head and neck positioning in awake subjects. Laryngeal and tracheal airway segments have been examined similarly.

Although airflow measurements can be made with either a face mask or a plethysmograph, there are situations in which one method is preferable to the other. For example, as mentioned above, the plethysmograph offers distinct advantages in diagnostic nasal patency measurements, whereas a face mask is more convenient than a plethysmograph for sleep and field studies. The circuitry and the range of the flow transducer in the Toronto transducer box assembly accommodate to either a plethysmograph or a mask system by appropriate calibration.

In addition to the investigations already described, the Toronto plethysmograph has been used also for the following.

1. Measurement of minute ventilation and tidal volume with rest and exercise.
2. Oronasal breathing. Effects of exercise and of nasal obstruction.
3. Evaluation of mask pneumotachometers, thermistors, thermoelectric couples, and inductive vests.
4. Assessment of resistance to respiratory airflow of industrial masks.
5. Assessment of phonatory airflow and subglottic pressures.
6. Assessment of patency of oral, pharyngeal, laryngeal, and tracheal airway segments.
7. Lung volumes, flow-volume loops, expiratory flow-volume curves, and other pulmonary function tests.
8. Laryngeal resistance (tracheal puncture or tracheostomy opening).

In the Toronto laboratories, face masks have been found more convenient for the following.

1. Studies of breathing in sleep, snoring, and hypopnea.
2. Studies of effects of posture on patency of pharyngeal and other airway segments.

We have used much smaller head-out plethysmographs for infant and animal studies.

Acoustic Reflection. Acoustic reflection is employed for assessment of airway dimensions. Measurements of pharyngeal, laryngeal, and tracheal airways have been performed extensively in Toronto and other centers for several years, and acoustic rhinometry, although a relative newcomer, has also achieved a well-established position in the field of nasal lumen studies.

In conclusion, it is the authors' hope that in addition to providing guidance in the use of the Toronto Systems, this manual will contribute to wider recognition of the authenticity of rhinomanometry and acoustic rhinometry and will point to their specific roles in objective assessment of nasal patency, not only in the research laboratory, but as clinical procedures of importance to effective patient care.

VALIDATION

Head-Out Body Plethysmograph. Volumes of expired air collected in a Douglas bag from subjects seated in the plethysmograph and measured with a spirometer have been shown to correspond closely with values obtained by means of the computer-assisted plethysmographic system over a wide range of minute ventilations.

Digitization. Fourier transformations and statistical studies of rhinomanometric data demonstrate that a sampling rate of 50 Hz is adequate for measurement of the parameters obtained from breathing signals.

Dacron Mesh. A 400-mesh Dacron or nylon filter material provides a resistor that performs as a laminar flow element for both the mask (resistor area 25 cm^2) and the plethysmograph (resistor area 150 cm^2), since measurements of differential pressures across each resistor have been shown to vary in a linear manner with airflow well beyond the breathing range.

Mask. Nasal resistance values were determined from subjects seated in the plethysmograph while wearing a carefully applied modified CPAP mask pneumotachometer. Two separate data acquisition Toronto Systems, calibrated with strict accuracy, were employed for simultaneous measurement of plethysmograph and mask pneumotachometer respiratory airflows. Nasal resistance values over a wide range were obtained simultaneously from both systems and found to be in close agreement.

Catheters. Catheters of small internal diameter can impair conduction of airway pressures, and catheters of large external diameter can obstruct the airway. Rhinomanometric measurements with catheters of differing diameters have demonstrated that 8F infant feeding catheters minimize these handicaps ef-

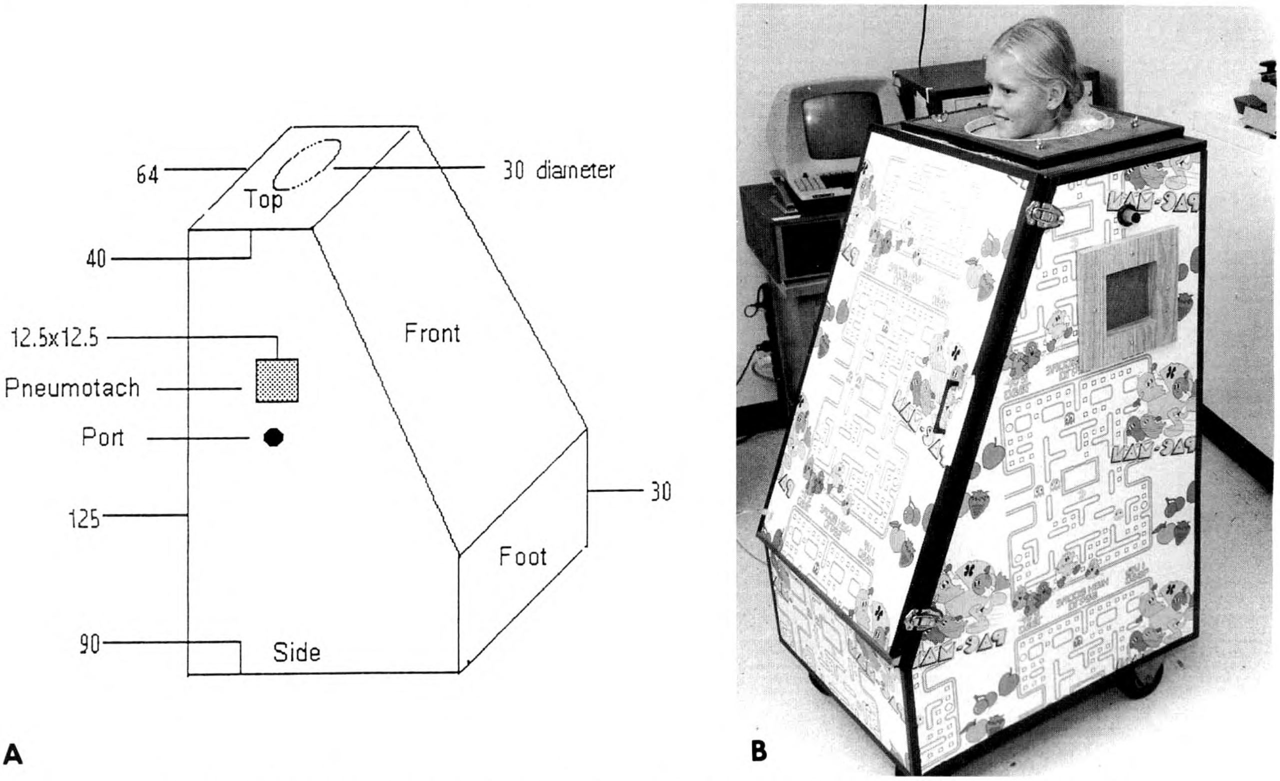


Fig 6. Head-out body plethysmograph with dimensions in centimeters. A) Diagram. B) Photograph.

fectively, and their laterally placed distal orifices also minimize accelerative effects of the airstream.

System. Monitor display of computer output has demonstrated that the complete data acquisition system, from plethysmograph (or from mask) to monitor, functions in a linear manner to the application of a series of measured airflows extending well beyond the range of resting breathing. These results indicate also that inevitable small leaks from the plethysmograph (which are included in flow calibration) do not corrupt flow measurements. Nevertheless, it is good practice to check the integrity of the seals and restore them if in doubt.

Similarly, a series of pressures measured by an inclined fluid manometer are represented by the system in a linear manner.

The frequency response of the plethysmograph was tested at high frequencies generated by a loudspeaker and at lesser frequencies by means of a piston pump and found to be adequate for measurement of breathing signals.

Acoustic Rhinometer. The Eccovision literature should be consulted. It is of interest to note the apparent similarity of results obtained from centers using acoustic rhinometry systems of different manufacture.

DESCRIPTION AND SOURCES OF EQUIPMENT

Inquiries and Rheomanometry Consulting Services. Victory Biomedical Inc, 350 Greenfield Ave, Willowdale, Ontario, Canada M2N 3E8; phone: (416) 221-4847; fax: (416) 221-0907; e-mail: victory@interlog.com.

Transducers. Max J. Kopp, Exec VP Sales, Vali-

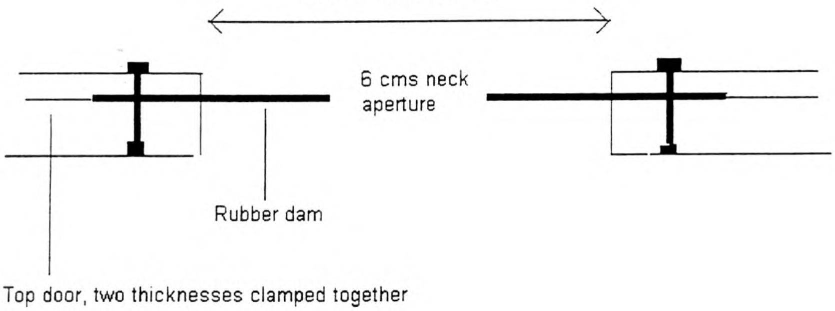


Fig 7. Replaceable rubber dam neck seal incorporated in top door of head-out body plethysmograph.

dyne Engineering Corp, 8026 Wilbur Ave, Northridge, CA 91324; phone: (800) 423-5851; fax: (818) 886-6512; e-mail: sales@validyne.com; website: http://www.validyne.com.

Rhinomanometer. Rhino-Med Research, 960 Lawrence Ave W, Ste 406, Toronto, Ontario, Canada M6A 3B5; phone: (416) 781-4000; fax: (416) 781-5402; e-mail: romanc@interlog.com.

Plethysmograph. Simple construction with laminated particle board approximately 18 mm ($^3/_4$ in) thick. Piano hinges for top and front doors. Door seals of closed-cell foam strips. Dimensions are not critical, but favorable aerodynamic characteristics are inversely proportional to enclosed volume (Fig 6).

The neck seal, with a central orifice of 6-cm diameter, consists of $^1/_{16}$-in rubber dam sandwiched between plywood sheets that constitute the top door. It can be easily replaced by release of clamping bolts (Fig 7).

Mask. See modification by Victory Biomedical Inc (Fig 2). Supplier: Respironics Inc, 1001 Murry Ridge Dr, Murryville, PA 15668-8550; phone: (800) 245-2767.

Dacron Mesh. Laboratory filter 400 mesh. Supplier: Hoskin Scientific, 4210 Morris Dr, Burlington, Ontario, Canada L7L 5L6; phone: (905) 333-5510.

Catheters. Infant feeding catheter 8F, 35-cm length, distal lateral orifices. Supplier: Ingram & Bell, 20 Bond Ave, Toronto, Ontario, Canada M5B 1L9; phone: (416) 444-7381.

Dental Dam. Gum rubber $^1/_{16}$-in thick. Supplier: Ontario Rubber, 281 Ambassador Dr, Mississauga, Ontario, Canada L5T 2J3; phone: (905) 564-6890.

Sealing Gel. Water-soluble lubricant gel is much more convenient in use than petroleum jelly. EcoGel 400 is fabricated for the Toronto System of acoustic rhinometry. Supplier: Eco-Med Pharmaceuticals Inc, 5775 Atlantic Dr (Unit 6), Mississauga, Ontario, Canada L4W 1H3; phone: (905) 564-6633.

Acoustic Rhinometer. Eccovision acoustic rhinometer. Supplier: E. Benson Hood Laboratories, Inc, 575 Washington St, Pembroke, MA 02359; phone: (800) 942-5227 or (617) 826-7573; fax: (617) 826-3899.

Computer. IBM 386 equivalent or better.

THE PLACE OF OBJECTIVE TESTING IN CLINICAL RHINOLOGY

J. S. Chapnik, MD, FRCSC
(by invitation)

The time-honored method of assessing the nasal airway consists of a history, physical examination, and objective testing. A number of simple, somewhat objective office tests have been employed in the past. A wisp of cotton held below the nose in the airstream moves to and fro during inspiration and expiration. Its extent of excursion can be recorded subjectively by the examiner (for what it is worth). Each side of the nose can be examined separately and the findings recorded. Similarly, the area of condensation on a cold mirror or metal tongue depressor held in front of the nares during expiration can be measured and similarly recorded. Both of the above tests produce a simple, primitive quantification of nasal airflow. The Cottle maneuver (retraction of the nasolabial fold upward) is an objective qualitative test of nasal valve function that is easily performed in routine office assessment.

The introduction of sophisticated, precise, objective measurements of nasal respiration has improved our understanding of nasal function. Rhinomanometry measures the resistance to nasal airflow in centimeters of water per liter per second (×0.1 pascals per cubic centimeter per second). This is a physiological test. By conducting the examination before and after topical nasal decongestion, one can deduce whether the obstruction is structural or mucosal in nature. Furthermore, if the test is conducted before and after mechanical retraction of the nasal valve, one can also deduce the degree of obstruction attributable to the nasal valve on one or both sides. The head-out body plethysmograph with pernasal intubation avoids distortion of this critical valve area.

Acoustic rhinometry is an objective method of measuring nasal anatomy, specifically, the minimal cross-sectional area of any segment of the nasal airway from the anterior nares to the posterior choanae. As with rhinomanometry, each side can be measured separately. Since measurements cephalad to the narrowest point of the nose are imprecise, this test is particularly effective for measurements in the anterior nose and, specifically, the critical nasal valve area. Recent improvements in the technique of acoustic rhinometry with the introduction of graduated nasal adapters, a head (chin and forehead) stabilizer, and excellent nasal gels to prevent sound leakage between the nostril and the adapter have resulted in improved reliability and reproducibility of results.

Rhinomanometry produces physiologic information regarding nasal function analogous to the audiometric information used in assessing otologic function. On the other hand, acoustic rhinometry provides anatomic information analogous to that provided by a radiograph. The combined tests therefore provide the clinician with both anatomic and physiological objective information. These results can be used for documentation before and after all treatments of nasal obstruction. Since factors other than mechanical or mucosal obstruction, such as heat, humidity, and pollutants, can affect the subjective sensation of nasal patency, objective methods of measurement assist the clinician in deciding on appropriate therapy.

We utilize objective testing in three major roles: routine rhinologic practice, research, and medicolegal purposes. Objective testing is specifically applied in clinical rhinology in the differential diagnosis and management of such common disorders as vasomotor rhinitis, nasal allergy, and deviated nasal septum.

Objective testing is of particular value in assessing those patients who have minimal findings on physical examination. In this group, objective testing is most helpful in decision-making. Minor changes in the nasal valve area can produce significant subjective inspiratory difficulty, which can be confirmed by objective testing. Such individuals will benefit from appropriate medical (topical steroids, hyposensitization) or surgical (septoplasty, rhinoplasty, cryotherapy, submucosal diathermy, partial turbinectomy) therapy. On the other hand, if the complaint of nasal obstruction cannot be substantiated by either physical examination or objective testing, the surgeon is alerted and the patient is not subjected to unnecessary or inappropriate treatment. Most important, the routine employment of objective quantitive assessment will result in improved understanding and management of nasal disease in general and the individual patient in particular. In those patients whose history, physical examination, and objective tests all indicate obstruction, objective testing (such as audiom-

---

Dr Chapnik is Associate Professor of Otolaryngology, Active Staff, Mount Sinai Hospital, and Director, Saul A. Silverman Airflow Laboratory and Clinical Investigation Unit, Mount Sinai Hospital, Toronto, Canada.

etry) is useful for confirmation and documentation. I now employ objective testing prior to all nasal surgery, even when the obstruction is self-evident. Given my confidence and reliance on rhinomanometry testing, just as I would not consider operating upon a patient's ear without a preoperative audiogram, similarly, I would not carry out nasal surgery without this preoperative test. The final role of acoustic rhinometry has not yet been defined, but I am impressed by its potential. I agree with the following solicited comments.

"General nasal inspection, endoscopy, rhinomanometry and acoustic rhinometry before and after decongestion to assess nasal patency in each patient before surgery...allows me to tailor surgery more individually." (Prof Dr W. Mann, Director, Hals-, Nasen- Ohrenklinik und Poliklinik, Johannes Gutenberg-Universitat, Mainz, Germany)

"Acoustic rhinometry...should be regarded as complementary...response to therapy can be monitored...excellent resolution...subtle changes may be documented...it is my expectation that it will enter routine clinical practice." (Valery J. Lund, MS, FRCS, FRCS Ed, Professor of Rhinology, Royal National Throat, Nose and Ear Hospital, London, England)